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CONGENITAL CYSTIC DILATATION OF THE BILE AND PANCREATIC DUCTS

NECROPSY THIRTEEN YEARS AFTER HEPATICODUODENOSTOMY

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The case here described was previously reported [1] after relief of biliary obstruction by operation for congenital cystic dilatation of the common bile duct.

Later, diabetes developed, and finally hypertension with nephrosclerosis led to death. Necropsy showed cystic dilatation of the bile ducts and both pancreatic ducts, with many obstructive cysts in the latter and a hepaticoduodenostomy opening which had functioned normally for over thirteen years.

Congenital cystic dilatation of the common bile duct is characterized clinically by symptoms of intermittent or chronic obstruction. The onset usually occurs in infancy or early youth, with intermittent attacks of acute abdominal pain. It is usually followed by jaundice and by a palpable mass in the right upper quadrant of the abdomen.

Pathologically there is cystic dilatation of the common duct with evidence of a noninflammatory stricture or atresia near the outlet. Similar changes may involve the entire biliary duct system and both pancreatic ducts, as in the case to be reported.

REPORT OF A CASE

Mrs. S., aged 49 years and 10 months, was admitted to the Presbyterian Hospital on Nov. 6, 1922. She complained of attacks of colicky pain in the upper part of the abdomen. Such pain, with nausea or vomiting, had followed ingestion

† Dr. McWhorter died Oct. 16, 1938.

1. McWhorter, G. L.: (*a*) Congenital Cystic Dilatation of the Common Bile Duct, Arch. Surg. **8**:604 (March) 1924; (*b*) Preventive Surgery of the Pancreas and Bile Ducts, Illinois M. J. **47**:128 (Feb.) 1925; (*c*) Results of Reconstruction of the Common Bile Duct: A Case Eight Years After Hepatico-Duodenostomy for Congenital Dilatation of the Common Bile Duct; Recent Diabetes Mellitus, S. Clin. North America **12**:159 (Feb.) 1932.

of food for practically all of her life. The severe attacks were often followed by jaundice, which at times persisted for years.

According to her mother, these acute attacks of pain were first noticed at the age of 6 months and continued to occur in association with jaundice until the patient was 7 years old. During the attacks she often lay doubled up with her face down, and since the pains became worse on sitting she rarely attended school. She was a thin and delicate child and was never able to run and play.

From the age of 7 until her first pregnancy, at 19, the attacks of pain were less severe, but even then she was able to eat only small amounts at a time.

During her pregnancies the attacks of pain were worse after the fourth month, and they became more severe after the birth of her seventh child, eleven years previous to her admission to the hospital.

The menses had become irregular four years previously; none had occurred during the last year. Since then the attacks of pain had been worse and had occurred about every three or four weeks.

The acute pains started in the epigastrium. They occurred usually after meals, but sometimes they began at other times when the patient was working. They extended to the right upper quadrant of the abdomen and frequently radiated to the lower angle of the right scapula. They were sometimes followed by vomiting or chills, which in turn were followed by perspiration, but when the colicky pain stopped the patient would usually feel well.

A hypodermic injection had been necessary for relief of pain three or four times a year during the last fifteen years and more frequently during the last year. Because eating usually brought on pain or distress she frequently took only a cup of tea and a piece of bread.

There had been no other illness, and she had not had any children's disease. There was no history of a similar condition in her family. She had three brothers, four sisters and seven healthy children.

Fourteen years previously she had been operated on elsewhere, and drainage of the gallbladder had been done. Immediately after the bile stopped draining, however, the attacks recurred.

Physical examination showed a white woman of small stature, deeply bronzed from long-existing jaundice. Her weight was 95 pounds (43.2 Kg.), which was normal.

The abdominal wall was relaxed except in the right upper quadrant, where there was a palpable subcostal mass which could not be definitely outlined owing to moderate tenderness and rigidity. Otherwise the findings were normal.

The blood pressure was 178 systolic and 110 diastolic, but five days previously, during an attack, it had been 132 systolic and 60 diastolic, with a pulse rate of 72.

Examination of the gastric contents after an Ewald meal showed normal findings.

Roentgenograms of the urinary tract and the gallbladder region showed no abnormality except for several small dense calcified areas near the spine, which were thought to be in the pancreas.

A clinical diagnosis of obstruction of the common bile duct, probably due to calculi, was made.

Operation was performed on November 7. A large cystic dilatation of the common bile duct was found, which extended behind the duodenum and was connected to it by one short, friable, narrow-strictured segment of duct, which was not surrounded by pancreatic tissue. This tore off from the sac when it was freed. It was left attached to the duodenal wall, but it was so small that no lumen could be found by probing.

The gallbladder was small, with a thick, muscular wall. It was attached near the upper end of the dilated common duct. There were a few small, black, uniformly round calculi in the common duct, but there were none in the gallbladder. When the dilated intrahepatic ducts were explored, similar calculi weighing about half an ounce (15 Gm.) were removed.

The head of the pancreas was in normal relation to the duodenum. It felt firm and sclerotic, and several hard areas could be palpated.

The cystic common duct together with the gallbladder was removed, and the end of the dilated hepatic duct was anastomosed directly to the duodenum, which was sutured to the round ligament to relieve tension. Two cigaret drains were inserted.

Pathologic examination showed that the excised large cyst was formed by the dilated common bile duct, which joined the cystic duct and the hepatic duct at the upper end. The muscles of the gallbladder wall were hypertrophied, and there was normal epithelium in some areas, while other portions showed desquamation.

The wall of the dilated common duct consisted of fibrous tissue, with no muscle. The epithelium was absent, but there was no evidence of inflammation, which indicated that the desquamation had occurred during preparation of the section.

There was ½ ounce (15 cc.) of small, shotlike black pigment stones which were not opaque to the roentgen ray.

A fragment of liver attached to the gallbladder showed a moderate amount of congestion with many round and a few polymorphonuclear cells but no evidence of suppuration or cirrhosis.

Convalescence was uneventful except for a duodenal fistula which developed on the twelfth day and healed in two weeks. After the operation the patient was able to eat regular meals without distress or pain for the first time in her life.

One year later she had gained 20 pounds (9 Kg.) in weight and had no complaints, although she had been doing all of her own housework.

Fluoroscopic examination of the stomach was made, and roentgenograms were taken after ingestion of a barium sulfate meal at twenty-five days, at one year and at seven days after operation. All showed dilatation of the intrahepatic bile ducts, especially of one to the left lobe, but there was no evidence of stenosis at the hepaticoduodenostomy stoma (figs. 1 and 2). Roentgenograms taken twenty-four hours after ingestion of the barium meal revealed only traces of barium remaining in the intrahepatic bile ducts.

In May 1930, seven and one-half years after the operation, the patient reentered the hospital, suffering from severe diabetes with loss of weight and appetite. There was no complaint of her old attacks of pain or jaundice. At times, when bending over at housework after meals, she would have some distress and tenderness in the upper part of the abdomen, but it may have been partly due to constipation. The icterus index of the blood was normal. The blood pressure was 190 systolic and 80 diastolic.

A strict diabetic routine was prescribed, which required the continued use of insulin. The patient continued to do her housework except during a severe attack of bilateral lumbosacral neuritis which developed seven months later and persisted for several weeks.

In May 1935, about nine months before her death, she reentered the hospital, complaining of feeling sleepy during the daytime. She was given a stricter diabetic diet, with larger doses of insulin. The urine showed a moderate amount of albumin. She felt better after this and continued to do her own housework. There was some gain of weight.

In October she reported having gained some weight but had no complaints except for trouble with her vision.

About December 26 she became too weak to do her housework and remained in bed most of the time. Her appetite was poor, and she became restless.

Examination on Jan. 7, 1936, revealed physical weakness. There was enlargement of the heart to the left, with a marked systolic murmur and an occasional extra systolic beat. The blood pressure was 260 systolic and 140 diastolic. The pulse rate was 96. Since leaving the hospital she had completely lost vision in the right eye and could just see fingers with her left; this condition was due to cataracts. There was no tenderness or palpable enlargement of the liver, and other physical findings were essentially normal. The urine was alkaline, had a specific gravity of 1.012 and contained a large amount of albumin. There was a large amount of sugar, in spite of the use of insulin and a greatly restricted diet.

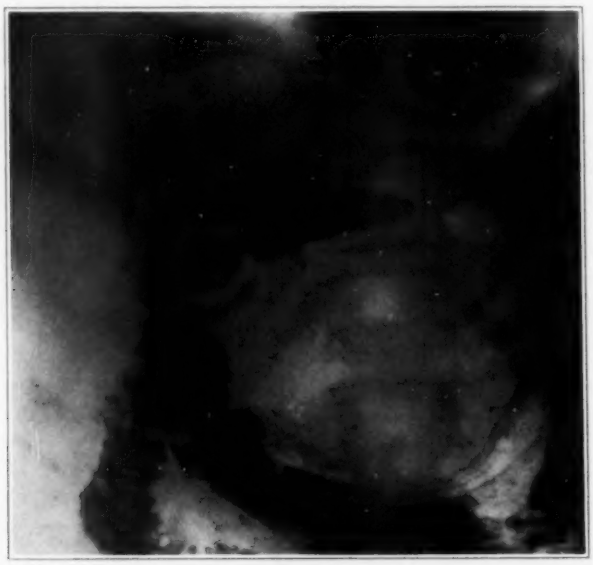

Fig. 1.—Branches of the dilated hepatic bile ducts after postoperative ingestion of a barium meal.

The patient gradually became weaker and died with symptoms of uremia on February 2, at the age of 63 years, over thirteen years after permanent relief of biliary obstruction by a hepaticoduodenostomy.

Necropsy was limited to the abdomen. The cadaver had been previously embalmed.

There were many adhesions beneath the operative scar. The liver weighed 1,075 Gm. and was normal in position, shape and size, but it was densely adherent to the duodenum at the site of the hepaticoduodenostomy. The gallbladder had been previously removed.

The head of the pancreatic mass appeared normal in size and shape, but it felt sclerotic, and the calculi could be palpated as several hard nodules. One large and several small cysts were observed involving the greater part of the pancreas. After evacuation of the cystic contents the pancreatic mass weighed 90 Gm.

The adrenal glands were both definitely enlarged. The kidneys appeared slightly smaller than normal, and the surfaces made by section showed narrowing of the cortex.

When the duodenum was opened the anastomosis to the hepatic duct, made in 1922, was observed 8 cm. from the pylorus. There was no narrowing of the opening, which was 1.1 cm. in diameter and was the same size as that part of the hepatic duct (fig. 3).

Proximal to the stoma was a redundant fold of the duodenal mucous membrane, which might have diverted some of the duodenal contents from the hepatic duct.

There were two dilated duct branches to the right lobe of the liver, which measured 8 cm. in length and 1.8 cm. in diameter. There were two large branches

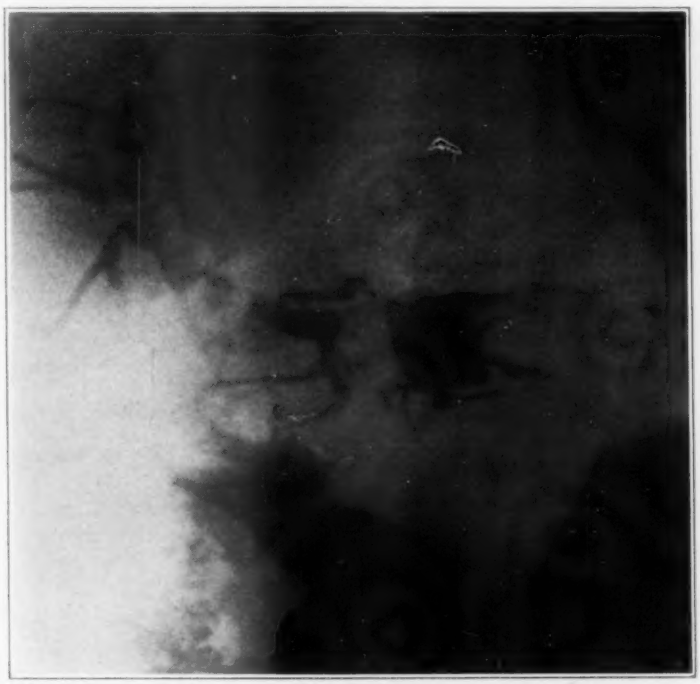

Fig. 2.—Barium after rapid passage into the peripheral bile ducts. The largest cystic dilatation occurred in a branch to the left lobe. After twenty-four hours only traces of barium remained in the ducts. Roentgenograms taken one month, one year and seven years after operation showed the same conditions.

to the left lobe. The largest measured 3.5 cm. in diameter and 8 cm. in length. It ended beneath a fibrous wall 2.5 cm. across, which appeared on the upper surface of the left lobe. The lower second branch was 7 cm. long, with a diameter of 1.3 cm., and gave off a branch almost as large. All of the large ducts gave off small peripheral branches which were moderately dilated. The dilated main bile ducts were sacculated and cystic in shape, with noticeable narrowing at their junction with other ducts, but there were no true cysts in the liver.

The minor pancreatic duct entered the duodenum 10 cm. from the pylorus, opposite the hepaticoduodenostomy stoma. The papilla was closed in a normal

manner but admitted a probe 2 mm. in diameter, and the duct passed through the wall for a distance of 1 cm. The duct was normal, smooth and regular until it reached a point 1 cm. outside the duodenum, when the lumen became irregular and sacculated, with incomplete narrowing at intervals. There were two main irregularly dilated branches of minor duct extending into the pancreatic mass, which contained seven rough, irregular calcareous calculi opaque to the roentgen rays. There were also several small fragments. The largest measured 1 by 0.5 cm. and was S shaped to conform to the shape of the dilated duct. There were a number of smaller branches ending in dilated pockets, while one small, irregularly stenosed duct approximated a branch from the major duct about 2 cm. from the major papilla.

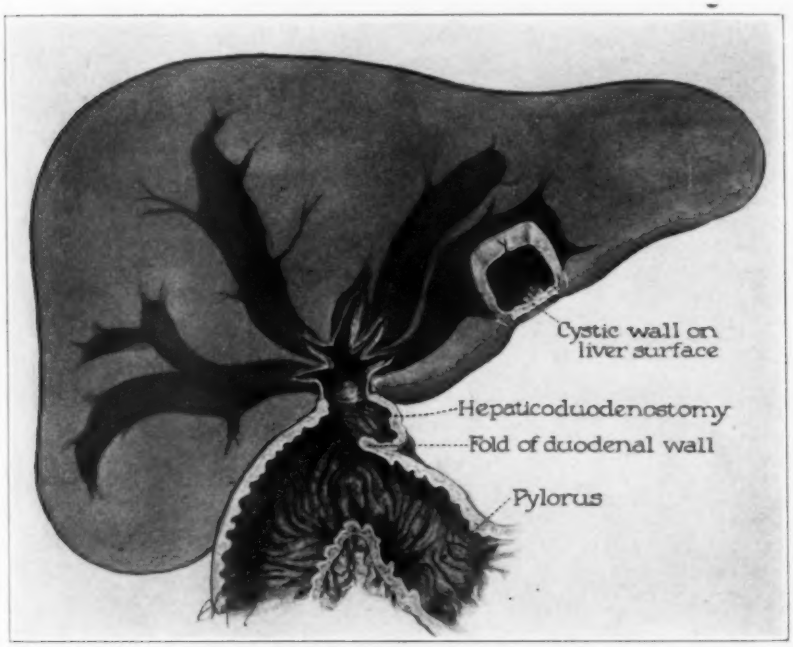

Fig. 3.—Dilatation and cystic degeneration of all the major intrahepatic bile ducts as well as the previously excised common duct. The cystic left anterior branch extended to the surface of the liver. The dilated smaller ducts were not included in the drawing but are well shown in the roentgenograms taken after ingestion of a barium meal (fig. 2). There was no evidence of stricture of the hepaticoduodenostomy stoma or complications over thirteen years after operation.

The papilla of the major duct was normal in appearance and location, 5 cm. below the minor duct, and admitted a probe 2 mm. in diameter. In spite of careful search there was no evidence of a separate papilla for the terminal end of the common bile duct or where it formerly joined the pancreatic duct. The major duct extended 1.5 cm. within the duodenal wall and 5 mm. beyond it with a perfectly normal size and appearance, when it became cystic, with a thinner wall, 2 cm. from the papilla at the same point as on the minor duct. The junction of the stenosed segment of the excised choledochus cyst was probably near the

terminal end of the dilated extraduodenal portion of the pancreatic duct. The extraduodenal junction of the common bile and pancreatic ducts, as well as their exit as separate ducts and papillae, has been observed in reported cases of choledochus cyst.

One of the first branches of the major pancreatic duct was completely stenosed, forming a large retention duct cyst with a smooth wall and occupying a large portion of the body and tail. The collapsed cyst, which had contained a clear, mucus-like material, measured 3 cm. in diameter and 9 cm. in length. Three or four small, dilated short ducts which could be probed entered the large cyst from the surrounding thin layer of the pancreatic mass.

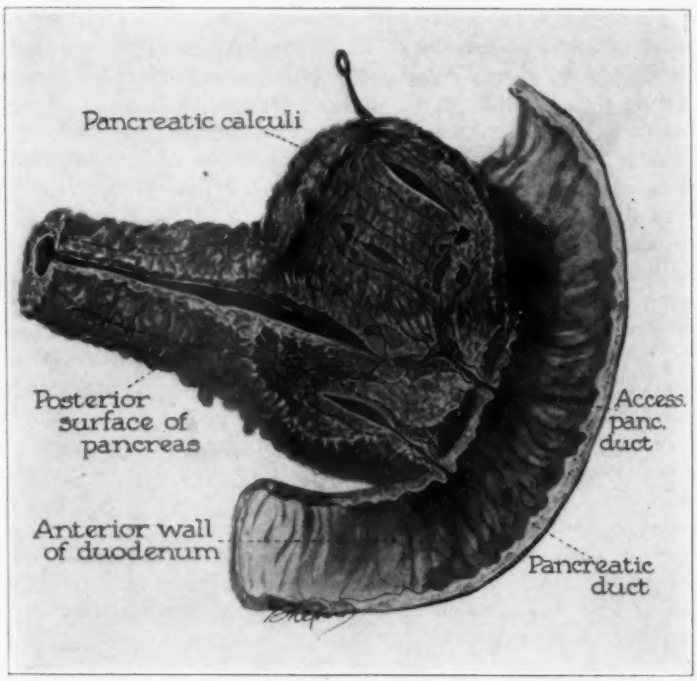

Fig. 4.—Major and minor pancreatic ducts involved in saccular dilatations and stenosis, except for their terminal 2 cm. and papilla, which were normal. Multiple calculi but no cysts occurred along the dilated saccular branches of the minor duct while retention cysts but no calculi occurred along the major duct. The parenchyma was replaced almost completely by fat and fibrous tissue.

There were three or four similar but small retention cysts distal to other stenosed branches of the major duct in the head of the pancreas, but there were no calculi in any branches of the major duct.

All microscopic sections were reviewed by Dr. Carl Apfelbach, pathologist at the Presbyterian Hospital.

Microscopic sections of the liver showed no evidence of damage or cirrhosis, and there was no dilatation or proliferation of the interlobular bile ducts. In a few places a minimal number of plasma and lymph cells were observed. There

was some postmortem dissociation of the hepatic cords, and there were occasional areas with slight fatty changes in the liver cells.

Sections of the dilated main intrahepatic bile ducts were cut, with adjacent liver tissue. The cystic walls were lined with columnar epithelium, although in places it evidently had been detached in preparation since there was no inflammatory reaction beneath the membrana propria. No muscle tissue was observed in the wall of these dilated ducts, which was composed of a wide layer of fibrous tissue. Near the largest left duct there was a large artery, and in places, parallel to it, there were numerous round and irregularly oval structures lined by cuboidal epithelium, which resembled tortuous crypts or hyperplastic glands. Serial sections showed that these structures gradually approached the dilated bile ducts, and at points their lumens were connected with the ducts. There were a few small areas of plasma and lymph cells along the walls of the dilated bile ducts.

Microscopic sections from the head of the pancreas about the branches of the major ducts showed only one round glandlike area to several low power fields and not more than ten to a whole section. Most of these areas were definitely islands of Langerhans, having a cordlike appearance, although one or two somewhat resembled acini; they had the general appearance of islands compressed by surrounding fibrous tissue. The pancreas was almost completely replaced by fat and fibrous tissue.

The wall of the large retention cyst showed absence of an epithelial layer. This also was probably caused by preparation of the sections since there was no round cell infiltration or any sign of inflammation along the thick fibrous wall.

There were no retention cysts along the dilated branches of the minor pancreatic duct, which contained calculi. In the adjacent pancreatic mass there were occasional islands of Langerhans and a few dilated and small ducts or acini lined with columnar epithelium and surrounded by fibrous tissue. Outside these ducts there were several areas consisting of a few lymphoid and numerous plasma cells, as contrasted with the branches of the major duct and the retention cysts, about which there was no inflammatory reaction.

Microscopic sections of the kidneys showed numerous hyalinized glomeruli and atrophy of approximately 15 per cent of the convoluted tubules. There was hypertrophy of the tunica media of the arcuate arteries, and in other blood vessels there were hyalinization and proliferation of fibrous tissue in the subintimal layer resembling arteriolosclerosis.

There was some inflammatory round cell infiltration where the tubules were undergoing destruction. The changes in the kidneys were typical of malignant nephrosclerosis with arteriolosclerosis of a moderate degree secondary to hypertension and arteriosclerosis such as is observed in cases of death from uremia.

COMMENT

Embryologic study of the liver and the pancreas is important to an understanding of the pathogenesis of congenital cystic dilatation and retention cysts of the bile and pancreatic ducts.

The liver is the first gland to develop and arises from the ventral anlage at about the same time that the dorsal anlage of the pancreas appears. The caudal part of the ventral anlage is hollow and gives rise to the gallbladder. It becomes constricted below by a narrow, solid cord of cells which later form the common duct and are attached to the anlage of the hepatic duct.

Two diverticula appear, one on each side of the common bile duct. That on the right becomes constricted into a cord of cells which becomes the pancreatic duct.

According to some investigators, the pancreatic evaginations are hollow. Others believe that they are solid at first. The same uncertainty exists in regard to the later outgrowths or budding into a compound tubular gland.

The left diverticulum probably disappears [2] except when it may persist as accessory pancreatic glands or diverticulums along the gastrointestinal tract or in neighboring structures, such as the gallbladder.

The small pancreas developing from the ventral anlage fuses with the larger dorsal pancreas. The ducts anastomose until those from the ventral pancreas become the major ducts to the pancreas.

The anlage of the liver develops as a series of outgrowths into the channels of the omphalomesenteric veins in the ventral mesentery. There is a series of hepatic cell trabeculae the meshes of which are filled with a sinusoidal circulation of blood. In each cord of liver cells there is a bile capillary.[2]

Lewis [3] stated that bile capillaries are present in a 44 mm. embryo. It could not be shown whether they develop as peripheral outgrowths from the periportal bile ducts or arise within the cell trabeculae as blind tubes and later anastomose to them. The latter theory would explain more satisfactorily the lack of bile capillary involvement in cystic disease of the ducts.

The common bile, cystic and hepatic ducts early become surrounded by mesenchyme, which later spreads along the ramifications of the portal vein into the substance of the liver. By the third and fourth months the bile ducts, the branches of the hepatic artery, the nerves and the lymphatics have extended into the periportal tissue.

Disturbances in the development of the mesenchyme might produce cystic dilatation of the bile ducts, although the evidence suggests maldevelopment of the ventral anlage and, in the case presented, also the dorsal anlage.

In the 47 cases which I previously reviewed [1] there was no cystic dilatation of the pancreatic ducts or evidence of polycystic disease in the kidneys, in the liver or elsewhere.

There have been numerous case reports since then,[4] but in only 1 case, in which two openings were seen in the lower end of the chole-

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2. Bailey, F. R., and Miller, A. M.: Common Bile Duct: Recent Diabetes Mellitus, S. Clin. North America **12**:159 (Feb.) 1932; Textbook of Embryology, ed 5, Baltimore, William Wood & Company, 1929, p. 319.

3. Lewis, F. T., in Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 419.

4. Wilson, H. V.: Choledochus Cyst, J. A. M. A. **95**:399 (Aug. 9) 1930.

dochus cyst and a choledochoduodenostomy was performed with the development of a pancreatic juice fistula, did the surgeon believe that there was an associated pancreatic duct cyst.[5] However, the pancreatic duct frequently joins the common duct before reaching the duodenal wall which might explain the two openings and also the pancreatic fistula. In Schloessmann's case [6] there was a second small cystic dilatation between the large one and the extraduodenal normal part of the bile duct where it was joined by the pancreatic duct, which shows the multiplicity of the cystic changes.

The occurrence of multiple noninflammatory cystic changes in the bile and pancreatic ducts with retention duct cysts in the pancreas in this case [7] constitutes a previously unrecognized pathologic entity of undoubted congenital origin. This condition usually is limited to maldevelopment of a part of the ventral anlage, but it is also evident that both ventral and dorsal anlages may be similarly and simultaneously involved and that the condition may lead to multiple retention duct cysts, at least in the pancreas. It is entirely different from polycystic disease of the liver, pancreas and kidneys, and the conditions have not been reported together.

Since polycystic disease occurs in viscera which differ in embryonic development, one may understand that cystic disease of the bile and pancreatic ducts may result from a slightly different form of maldevelopment.

Polycystic disease of the kidneys is believed to be due to maldevelopment of the metanephros and the wolffian duct with failure of union of the proximal and distal portions of the tubules.[8] Polycystic disease of the liver is not frequent, while in the pancreas it is rare, although it may occur alone or associated with similar changes in other viscera.[9]

Congenital cystic disease of the bile or pancreatic ducts should be diagnosed only when there are clinical symptoms due to stenosis with some obstruction at the outlet or having characteristic pathologic findings. Recently, Koch [10] included under this classification a case of

5. Iselin, H.: Gemeinsame Cyste der Gallen- und Pankreaswege, Arch. f. klin. Chir. **145**:304, 1927.

6 Schloessmann: Beitrag zur Kenntnis der Choledochuscysten, Deutsche Ztschr. f. Chir. **109**:161, 1911.

7. McWhorter, G. L.: Cysts of the Pancreas, Arch. Surg. **11**:619 (Oct.) 1925.

8. McGregor, A. L.: Synopsis of Surgical Anatomy, ed. 3, Baltimore, William Wood & Company, 1936, p. 344.

9. Wood, H. G.: Polycystic Disease of the Pancreas: Report of a Case, Proc. Staff Meet., Mayo Clin. **11**:449 (July 15) 1936. Walters, W., in discussion on papers by Wood, Rynearson, Kepler and Walters and Mayo, ibid. **11**:458 (July 15) 1936. Nygaard, K. K., and Walters, W.: Polycystic Disease of the Pancreas (Dysontogenetic Cyst), Ann. Surg. **106**:49 (July) 1937.

10. Koch, F.: So-Called Choledochus Cyst (Idiopathic Congenital Dilatation), Hygiea **98**:577 and 608 (Sept. 15) 1936.

dilatation of the common duct with no obstruction found at the time and another case with an obstructing tumor of the papilla.

As to the cause, it has been suggested that the stricture of the terminal bile duct is a form of congenital atresia and that the dilatation is secondary to the incomplete obstruction. Beneke [11] found in a review of cases in which there was complete congenital obliteration of the common bile duct that the extrahepatic ducts were not dilated. There may be exceptions to this finding, as in the cases of Legg and Oxley.[12]

Budde [13] concluded that cystic dilatation of the common duct was secondary to primary diverticula of the pancreatic anlage and was similar to traction diverticula. In his case there was a diverticulum of the duodenum, into which the strictured common duct and the pancreatic duct both entered.

Morley [14] stated that a valvular obstruction of the bile duct just outside the duodenum results from deficient peritoneal fixation. Pavel [15] has suggested that spasm of the sphincter is the cause of congenital cystic dilatation of the common duct, but the evidence does not support this theory.

The absence of muscle fibers in the dilated ducts in my case may have been due to a congenital deficiency leading to dilatation or resulting from it. It is recognized that there may be a similar deficiency of smooth muscle in the presence of congenital hydronephrosis or hydronephrosis of acquired mechanical origin and that congenital defects of smooth muscle which occur in the wall of the arteries at the base of the anterior part of the brain may result in congenital aneurysms and later in hemorrhages.[16]

Another congenital factor may be maldevelopment of mesenchymal tissue about the bile ducts, of a segmental nature, leading to both stenosis and dilatation. Further understanding may depend on a complete knowledge of the embryologic development of the bile and pancreatic ducts.

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11. Beneke, cited by Roberts, E. D.: Un cas de dilatation kystique du canal cholédoque, Thesis, Lausanne, 1914.

12. Legg, J. W.: Congenital Deficiency of the Common Bile Ducts Ending in a Blind Sac; Cirrhosis of the Liver, Tr. Path. Soc. London **27**:178, 1876. Oxley, M. G. B.: Congenital Atresia of the Duodenal Opening of the Common Bile Duct in an Infant, Producing a Large Abdominal Tumor, Lancet **2**:988 (Dec. 8) 1883.

13. Budde, M.: Ueber die Pathogenese und das Krankheitsbild der cystischen Gallengangserweiterung; sogenannte idiopathische Choledochuscyste, Deutsche Ztschr. f. Chir. **157**:364, 1920.

14. Morley, J.: Congenital Cyst of the Common Bile Duct, with Report of Two Cases, Brit. J. Surg. **10**:413 (Jan.) 1923.

15. Pavel, I.: Jaundice Caused by Functional Obstruction, J. A. M. A. **110**: 566 (Feb. 19) 1938.

16. Apfelbach, C., pathologist of the Presbyterian Hospital: Personal communication to the author.

In the case here presented the maldevelopment of the bile ducts and both pancreatic ducts, not involving their dudoenal terminations, indicates the involvement of both ventral and dorsal anlages. This condition primarily apparently did not involve either the peripheral interlobular bile capillaries or the peripheral pancreatic ducts and acini although the latter secondarily were almost completely degenerated.

Symptoms of congenital cystic disease of the bile and pancreatic ducts were variable, owing to the differing degrees of stenosis and complications.

Clincially one must differentiate the symptoms of cystic disease of the ducts from obstruction of the common duct by calculi, inspissated bile or mucus, which may occur together with congenital stenosis [17] and from complete atresia of the ducts. The small stature of my patient was probably the result of a restricted food intake from infancy.

Pathologically such dilatation must be differentiated from dilatation of the common duct produced by an acquired obstruction.[18]

Clinically, it may be difficult to diagnose involvement of the pancreatic ducts either with or without true retention cysts. Large retention cysts may be palpable or may produce pressure disturbances, and there may be symptoms or laboratory evidence of complications or extensive degenerative changes. Calculi which may cause attacks of pain and evidence of inflammatory changes in the pancreas may be visualized by roentgenograms.

The fibrous and fatty degenerative changes in the pancreas with loss of function resulting from congenital occlusion of the ducts, the retention cysts and the obstructing calculi were probably contributing factors in the development of diabetes, arteriosclerosis, hypertension and nephrosclerosis leading to death, but there was no evidence of permanent disturbance of function or of pathologic change in the liver.

At the time of the hepaticoduodenostomy the patient was in no condition to withstand any operation on the pancreas even if it had been desirable. One should consider what benefits might have been obtained from drainage of the large pancreatic cyst by creation of an anastomosis with the small intestine or by removal of the calculi. If such an operation had been performed before extensive degenerative changes had occurred, some islands of Langerhans and some pancreatic function might have been preserved. However, the possible benefits, especially after a number of years, might be offset by the risk of operation.

In the 47 cases of cystic dilatation of the common bile duct which I reviewed in detail,[1] biliary cirrhosis was noted in 14; the liver was

17. Ladd, N. E.: Congenital Obstruction of the Bile Ducts, Ann. Surg. **102**: 743 (Oct.) 1935.

18. Counseller, V. S., and McIndoe, A. H.: Dilatation of the Bile Ducts (Hydrohepatosis), Surg., Gynec. & Obst. **43**:729 (Dec.) 1926.

normal in 12 and was not mentioned in 13, while in the others a moderate degree of hepatitis was described.

In contrast to this group with incomplete or intermittent biliary obstruction, Beneke [11] reviewed a series of cases with complete congenital obliteration of the common duct and reported observation of cirrhosis of the liver in all.

There have been few reports of cases with hepaticoduodenostomy of several years' duration for any condition, and necropsy observations have usually been reported on those in which the results were unsuccessful.

Normally the sphincter and papilla guard the bile ducts from ascending parasites, foreign bodies and infection.[19] Both clinical and experimental results of hepaticoduodenostomy have shown the dangers from stricture formation and ascending infection, although it is probable that the latter would rarely have occurred without biliary obstruction. Recent experimental work of Gentile [20] has indicated that danger of ascending infection in hepaticoduodenostomy in the absence of biliary stasis has been overemphasized. However, a certain amount of regurgitation of food through the stoma is always a potential source of infection and may produce mild attacks of inflammation in the ducts or liver, with complete recovery. In animals I have observed death following obstruction of the common duct by roundworms after experimental dilation of the sphincter with patency of the outlet.

Finsterer [21] stated that he has abandoned drainage of the hepatic ducts for anastomosis of the common duct to the duodenum in cases of multiple stones in the hepatic duct, in the presence of severe suppurative cholangitis and in the presence of absolute or relative stenosis of the papilla. He reported 80 cases with an increase of cures from 40 to 95 per cent for as long as ten years without ascending infection in spite of a wide anastomosis, which he sometimes demonstrated by roentgen ray visualization after administration of a barium sulfate meal.

The prognosis of cystic dilatation of the common bile duct without operation is usually bad. The friable condition of the stenosed terminal segment of the common bile duct and the surrounding edema in my case would indicate some inflammatory reaction during attacks of obstruction. This may explain the usual progressive nature of the stenosis and biliary obstruction in the absence of suppuration. In 48 cases [1] the

19. McWhorter, G. L.: The Surgical Significance of the Common Duct Sphincter, Surg., Gynec. & Obst. **32**:124 (Feb.) 1921.

20. Gentile, A.: Cholecystogastrostomy and Hepatitis: Experimental Study, Arch. Surg. **30**:449 (March) 1935.

21. Finsterer, B. F., in discussion on Bernhard, F.: Ueber neuere Gesichtspunkte aus der Chirurgie der Gallenwege, Arch. f. klin. Chir. **189**:81, 1937; abstracted, Surg., Gynec. & Obst. **65**:412 (Nov.) 1937.

operative mortality was 71 per cent, and all patients not operated on died. The high mortality after operation was due to the fact that most of the patients were emaciated and badly jaundiced.

In 22 cases exploratory operation, alone or combined with external drainage, resulted in death. Exploratory aspiration with leakage of bile and peritonitis occurred in 2 cases.

The mortality was fairly low in cases in which biliary drainage was obtained by an anastomosis of the cystic common duct to the duodenum at the first operation. In more recent operations by this method the mortality has been much lowered by earlier operation. However, the stoma must be adequate, as stenosis has resulted, producing attacks of pain and jaundice sometimes so severe as to require reoperation.

The operative treatment of choice is either to anastomose the common bile duct to the duodenum or to excise the dilated part of the common duct and anastomose the remaining end to the duodenum.

The former is the simpler and has a relatively low operative mortality, and it should be chosen when the patient is in poor condition, but the remaining cystic common duct may cause prolonged retention of food. This may lead to severe ascending cholangitis, as in the fatal case reported by Fowler,[22] in which a lateral anastomosis of an acquired dilatation of the common duct was made to the duodenum.

Complete or partial excision of the dilated common duct with an anastomosis of the stump to the duodenum may be chosen when the cystic dilatation is large and the patient is in good condition, since, as shown in the present case, there will be little retention of food and less danger of cholangitis.

Nonoperative treatment of the pancreatic duct calculi and retention cysts in this case had no obvious direct effect on the outcome, but the obstruction of the ducts by cysts and calculi undoubtedly produced degenerative changes in the pancreas, contributing to loss of function, diabetes and arteriosclerotic changes.

Indications for operation on the pancreas might result from pain from pancreatic calculi, secondary suppuration and physiologic or pathologic disturbances from retention cysts.

SUMMARY AND CONCLUSIONS

A necropsy report is made of a case of congenital cystic disease of the bile and pancreatic ducts.

This condition is shown to be a distinct congenital entity which may involve both ventral and dorsal anlages but is not to be confused with congenital polycystic disease of the liver or the pancreas.

22. Fowler, R. S.: Choledochus Cyst, Ann. Surg. **64**:546 (Nov.) 1916.

In this case the findings point to a congenital maldevelopment of anlages which form the bile ducts and both pancreatic ducts. In other cases these changes were largely limited to involvement of the extraduodenal portion of the common bile duct, although in some cases it distorted secondarily the intraduodenal portions by traction, distention or inflammation. Apparently in no instance were the peripheral capillary bile ducts involved. In the present case, the pancreatic acini and islands of Langerhans were almost completely degenerated, evidently as a result of congenital obstruction of the ducts and pressure by the retention cysts or of the presence of calculi.

The liver showed no evidence of cirrhosis, and no complications appeared for over thirteen years after a hepaticoduodenostomy, which is evidence that ascending infection will not necessarily result from the operation and that hepatic function may not be damaged in the absence of biliary obstruction, even with regurgitation of food into the intrahepatic ducts.

Through further knowledge and early clinical recognition a properly chosen operative procedure may lessen the dangers of this congenital condition at a minimum risk.

CLINICAL SIGNIFICANCE OF CALORIMETRIC CHANGES IN THE LOWER EXTREMITY

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Hesse [1] in 1929 directed attention to the occurrence of calorimetric changes in the skin of the lower extremity, resulting from irritation or pressure on the lumbar portion of the ganglionated cord and its connecting rami. Pressure or irritation affecting the lumbar portion of the ganglionated cord, whether it is of inflammatory or of neoplastic origin, may produce well defined changes in temperature of the skin of the corresponding lower extremity.[2]

The changes in temperature vary with the degree and type of pressure on the ganglionated cord. Mild pressure or irritation results in the appearance of increased vasoconstrictor phenomena in the corresponding lower extremity. Comparative estimations of the temperature of the skin of the lower extremity will disclose in such instances a decrease in temperature on the side on which retroperitoneal pressure is present. The increased vasoconstriction results in lessened blood volume and thus in lowering of the cutaneous temperature. Paralleling the changes in the surface temperature are changes in the sweat glands and in the erector pili muscles. In the stage associated with peripheral vasoconstriction, perspiration and the pilomotor reflex are increased.

When pressure on the ganglionated cord is sufficient to interrupt the conduction of all impulses that traverse the cord, persistent vasodilatation results, and the temperature of the corresponding lower extremity is elevated. During the stage of peripheral vasodilatation, perspiration

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1. Hesse, E.: Ein neues calorimetrisches, durch Druck auf den Sympathicus hervorgerufenes Symptom retroperitonealer raumbeschränkender Erkrankungen, Klin. Wchnschr. **8**:1360 (July 16) 1929.

2. Zaiceva, A.: Ueber das Hesse'sche Symptom bei Retroperitonealtumoren, Zentralbl. f. Chir. **59**:2685 (Nov. 3) 1932. Vinogradov, I. P.: Das calorimetrische Symptom Hesses bei Geschwülsten und anderen raumbeschränkenden Erkrankungen im Retroperitonealraum, Deutsche Ztschr. f. Chir. **246**:634, 1936.

and the pilomotor reflex are decreased. Additionally, the stage of vasodilatation shows an absence of the waves of spontaneous diminution of volume.[3]

The differences in temperature between the two extremities may range from 1 to 6 degrees C. (1.8 to 10.8 degrees F.). The difference in temperature encountered in the lower extremities during the stage of increased vasoconstriction is generally less than that observed during the stage of vasodilatation.

Determinations of temperature were carried out in the following manner: The lower extremities were examined for evidence of peripheral vascular disease which might influence cutaneous temperature. All 3 patients had adequate peripheral circulation. The lower extremities were exposed to room air, the rest of the body being covered only by a light sheet. Care was taken that there should not be any drafts or movements of air which might influence the temperature of one or both extremities. The temperature of the first and third toes of each foot was taken with an electrothermocouple at the start and at intervals up to thirty minutes' exposure to room air. It was assumed that at the end of thirty minutes the effect of previous warming of the extremities by bed clothes had been eliminated. In the absence of an electrothermocouple the temperature of the skin may be taken by the simultaneous use of two thermometers at corresponding sites on the lower extremity, preferably between the toes. Differences in temperature of the lower extremity of 1 degree C. (1.8 degrees F.) or more can be felt with the bare hand.

REPORT OF CASES

CASE 1.—E. H., a man aged 52, was admitted to the hospital on Dec. 29, 1935, because of severe constipation of two months' duration and cramps in the lower part of the abdomen for about three weeks. There had been no loss of weight. The most important finding at physical examination was a mass in the right lower quadrant of the abdomen, about 6 cm. square. It was hard, fixed and not tender. There was a small epigastric hernia. A barium sulfate enema revealed a complete obstruction to the barium at the proximal transverse colon. The diagnosis of the roentgenologist was carcinoma of the transverse colon. Laboratory studies gave normal results. The temperature studies were as follows:

Right Foot		Left Foot	
First Toe	Third Toe	First Toe	Third Toe
25.2 C. (77.4 F.)	23.5 C. (74.3 F.)	22.5 C. (72.5 F.)	21.5 C. (70.7 F.)

Laparotomy was performed by means of a transverse incision on the right side, at the level of the umbilicus. The posterior paries was found attached to a hard mass the size of a fist, apparently springing from the transverse colon. The mass was attached to the liver. There were nodules in the peritoneum. The mass

3. Bolton, B.; Williams, D. J., and Carmichael, E. A.: Sympathetic Ganglionic Responses in Man, Brain **60**:39 (March) 1937.

was partly freed but was found to be inoperable. A biopsy of material taken from the omentum revealed secondary carcinoma.

Comment.—In this patient the temperature of the extremity was higher on the side on which the lesion was present.

Case 2.—B. S., a man aged 65, was admitted to the hospital Jan. 8, 1936, because of vomiting after every meal and epigastric pain of several months' duration. There had been no loss of weight. About six weeks before admission the patient observed that the right thigh was larger than the left and was painful. He also had pain in the right lower quadrant of the abdomen. The medical history was irrelevant. On physical examination the only positive findings were tenderness to deep palpation in the right lower quadrant of the abdomen, varicose veins, especially on the right leg, and enlargement of the right thigh. No definite mass was palpated in the abdomen. Cystoscopic examination, retrograde pyelographic study and roentgenographic examination of the thigh gave negative results. A barium enema disclosed "the cecum lying unusually high, being apparently displaced upward by an intrinsic mass." The results of urinalysis, blood counts and chemical studies of the blood were normal. The surface temperature was as follows:

Right Foot		Left Foot	
First Toe	Third Toe	First Toe	Third Toe
30.2 C. (86.4 F.)	30.09 C. (86.2 F.)	24.8 C. (76.6 F.)	23.6 C. (74.5 F.)

Laparotomy was performed, and a mass of retroperitoneal lymph nodes was found lying against the sympathetic ganglions on the right side.

Comment.—If the temperature is higher on the affected side the ganglions are destroyed or impulses completely interrupted.

Case 3.—I. C., a man aged 26, was admitted to the hospital May 8, 1935, because of pain in the lower part of the abdomen and diarrhea since November 1934. He had had vague symptoms dating back to March 1933. The medical history revealed incision of a cervical gland at the age of 9 and also the development of a sinus in the left ankle in infancy, which was diagnosed as tuberculosis. On physical examination the outstanding finding was the presence of a mass palpable in the right lower quadrant of the abdomen. Digital rectal examination revealed a hard, fixed shelving against the anterior wall of the rectum. Sigmoidoscopic examination confirmed the presence of this bulge in the rectal wall, and beyond it, at the rectosigmoid junction, resistance was met. A barium enema likewise revealed an obstruction at the rectosigmoid junction. The diagnosis was carcinoma of the sigmoid or retroperitoneal sarcoma. Laboratory studies, including search for tubercle bacilli, all gave negative results. Temperature studies revealed the right foot to be distinctly warmer than the left.

Right Foot		Left Foot	
First Toe	Third Toe	First Toe	Third Toe
26.2 C. (79.2 F.)	25.8 C. (78.4 F.)	22.4 C. (72.3 F.)	21.7 C. (71 F.)

Laparotomy was then performed, and an enormously thickened terminal ileum was found. It was adherent to the peritoneum, the sigmoid flexure, the transverse colon and other structures. Twelve inches (30 cm.) of the terminal portion of the ileum and part of the cecum were resected. The patient had an uneventful convalescence and was discharged two weeks after operation. The pathologic

diagnosis was that of a chronic inflammatory process of the ileum. At the time of writing, three years after the operation, the patient has no symptoms. Temperature studies in 1938 revealed the right foot still approximately 1 degree C. (1.8 degrees F.) warmer than the left.

COMMENT

The clinical findings noted are in accord with the anatomic structures and physiologic functions of the affected parts. A brief discussion of the physiologic considerations is set forth.

The ganglionated cord lies fixed along the anterolateral surface of the vertebrae, and any pressure on the cord, such as may be caused by inflammation or by a neoplasm, may produce changes in the temperature of the ipsilateral lower extremity. The fixed retroperitoneal location of the ganglionated cord renders its component neurons and fibers readily liable to retroperitoneal irritation or pressure.

The function of the sympathetic innervation of the blood vessels is essentially tonic or excitatory. The ganglions of the lumbar portion of the ganglionated cord probably contain the cell bodies of the vasomotor postganglionic fibers which act as vasoconstrictors. The peripheral blood vessels receive their efferent innervation solely through the sympathetic system; their supply by parasympathetic fibers is still a moot question.

It is generally accepted that vasomotor responses are easier to obtain from the toes than from the fingers. Immersion of the lower extremity in water at 44 to 45 C. (111.2 to 113 F.) produces a sustained, widespread dilatation of the cutaneous vessels of the digits, and the resultant changes in the blood volume are greater in the toes than in the fingers. Similarly, peripheral sensory stimuli effect a greater degree of vasoconstriction in the toes than in the fingers. Examination of patients who have been sympathectomized for nonvascular diseases shows absence of spontaneous waves of diminution in the toes which would seem to imply that waves of diminution in the blood volume of the toe are an indication of vasoconstriction and are dependent on the integrity of the postganglionic fibers.

It is needful to bear in mind that pure ganglionic vasomotor responses do not occur. To effect a vasomotor response under normal conditions it is necessary for an afferent fiber to reach the spinal cord and within the central nervous system to be connected directly or indirectly by connector neurons to the cells in the intermediolateral column of the spinal cord, which give origin to the preganglionic fibers.

The postganglionic fibers in the case of the blood vessels are under the control of the regulatory, inhibitory preganglionic neurons. Thus, persistent dilatation of the blood vessels may result from destruction or pressure of the preganglionic fibers. Persistent dilatation of the vessels

of the toes may result from interruption of either the preganglionic or the postganglionic fibers to the toes.

One sometimes wonders whether the greater vascular stability of the upper extremity as compared with the lower extremity may not be the result of simultaneous action of two preganglionic fibers on a single postganglionic neuron, reenforcing or "stepping up" the inhibitory impulse. Perhaps the absence of a white rami communicans in the lower three lumbar nerves may account for this difference in vascular stability.

This calorimetric syndrome appears to be based on sound premises. Clinically it has received meager attention.

A lesion causing enlargement of the kidney, a lesion of the vertebrae, a retroperitoneal lesion (such as lymphadenitis, sarcoma or metastasis) or an intra-abdominal lesion associated with fixation of the posterior parietal peritoneum may produce irritation or pressure of the lumbar portion of the ganglionated cord. In brief, any lesion which causes pressure or irritation of the lumbar portion of the ganglionated cord may effect changes in the temperature of the ipsilateral lower extremity. Retroperitoneal lesions not infrequently present an obscure clinical picture, and any possible aid toward early diagnosis is worth while.

Comparative calorimetric studies of the cutaneous temperature of the lower extremities may be helpful not only in diagnosis but in localization of the lesion, since the changes occur on the side on which retroperitoneal pressure is present. In addition, information may be obtained as to the stage and progress of the lesion. Irritation or moderate pressure on the lumbar portion of the ganglionated cord produces peripheral vasoconstriction with its accompanying decrease in the cutaneous temperature on the side on which the retroperitoneal pressure is present. As the lesion increases in size, vasoconstriction is succeeded by vasodilatation, which is associated with elevation of temperature and absence of the waves of spontaneous diminution of volume.

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HISTOLOGIC AND HISTOCHEMICAL STRUCTURE OF THE NORMAL THYROID GLAND

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The study of the structure of the normal thyroid gland has been strangely neglected. So long as the morphologic character of the goitrous gland was just one more thing to quarrel about, this lack of knowledge of the normal gland was not a serious matter. Now that the relation of the goitrous gland to the heart has been abundantly demonstrated in the clinic, knowledge of the anatomy of the nongoitrous gland becomes an imperative necessity. The question is whether or not a nongoitrous gland may so degenerate as to affect the heart as a goitrous gland does. In order to answer this question it will be necessary to examine a large number of thyroid glands of nongoitrous persons.

Goiter is a clinical term. This becomes important in the morphologic study when one attempts to compare the nongoitrous and the goitrous gland. Even in the laboratory it is often a question whether a particular thyroid is goitrous. To determine this by weight alone is, of course, impossible. If one attempts to determine it by microscopic study one finds the dividing line equally indistinct. The confusion is heightened when one finds in a supposedly normal gland changes indistinguishable from those found in goitrous glands with associated cardiac symptoms which disappear when the gland is removed. This suggests the possibility that if one encounters in patients with nongoitrous glands cardiac disease identical with that found in association with degenerating goiter one must remove the thyroid gland in order to rescue the heart.

Clinically the presence of goiter is determined by palpation of the neck. Whether or not a diagnosis of goiter is made depends on the location of the gland, the type of patient and finally the "personal equation" of the examiner. Failure to diagnose a goiter clinically is never conclusive evidence that no goiter is present.

Rice [1] has presented a discussion of the normal thyroid gland. He has found the infantile gland divided into fields and the adult gland made up of acini of various sizes, lined by flat epithelium. He has

1. Rice, C. O.: Histologic Structure of the Normal Thyroid Gland: Variations and Their Significance in the Interpretation of Pathologic Conditions of the Thyroid Gland, Arch. Surg. **36**:96 (Jan.) 1938.

stated that in the gland of the aged the connective tissue septums again become prominent.

The present article is intended to be confirmatory and in a measure supplementary to that of Rice: confirmatory in the points previously mentioned; supplementary, chiefly because of the fact that I have given particular attention to a study of the colloid by means of tinctorial chemical tests. Studies by others have dealt chiefly with the epithelium. The varied and changed structure of the colloid seems to me to hold the key to what the gland is actually doing. "By their acts ye shall know them" is accepted by the ecclesiastic, the policeman and the physiologist. Why should the surgical pathologist not apply the same criterion? The present determinations indicate that such a study is particularly valuable, because it gives the investigator a new "slant" on the functions of the cell, or at least it helps him to determine when the cell ceases to function. First of all, a tinctorial study of the colloid compels one to doubt whether cells once quiescent become active again. That is to say, a "resting" cell is probably permanently functionless. If there is a return of function in the gland it is by the agency of newly formed acini.

My studies began forty years ago. I have endeavored to secure as much fresh material as possible, either in the course of operations in the cervical region or at autopsies on patients who had met violent death or who had died from some sudden complication, notably from hemorrhage. The purpose of thus selecting the material is to avoid confusion caused by changes in the structure of the thyroid, incidental to a terminal disease.

I was at first disposed to believe, from a study of this carefully selected material, that it differed in no way from that secured at routine autopsies. Apparently the disease which causes the death of the patient produces no regular change in the structure of the gland. However, a more extended study of autopsy material compels me to believe that at least exhaustive diseases, such as suppurations, may hasten the changes that one ordinarily finds in the glands of the aged. The structure is so variable in chronic disease as well as in old age that no definite conclusions can be reached. This is not surprising, because the calendar only in a general way indicates the actual age of the patient. Perhaps one is as old as one's thyroid gland. This problem is well worth further attention if physicians are to study the nongoitrous thyrotoxic heart.

Generally speaking, one can divide the study of the normal thyroid into three parts: the normal thyroid in childhood, the normal thyroid in maturity and the normal thyroid in old age.

Childhood may be made to include the period between the embryologic appearance of the gland and the end of puberty. Young folk in their teens regard themselves as mature, despite the opinion of their elders, and a study of their thyroids compels one to agree with them.

The characteristics of the immature gland are a relatively high epithelium and a thin colloid. Beginning as solid cell masses, acini gradually form, until after puberty few or no solid interacinal cell masses remain. In general, one may compare the gland in this early stage of its development with the thyroid of a patient with exophthalmic goiter. The nervous activity of the toxic stage compares well with the restlessness of childhood. A study of the thyroid provides an explanation. In both instances the acinal cells are cuboidal, even columnar, and the colloid is invariably thin. The height of the cells varies, but they are always at least as high as they are broad.

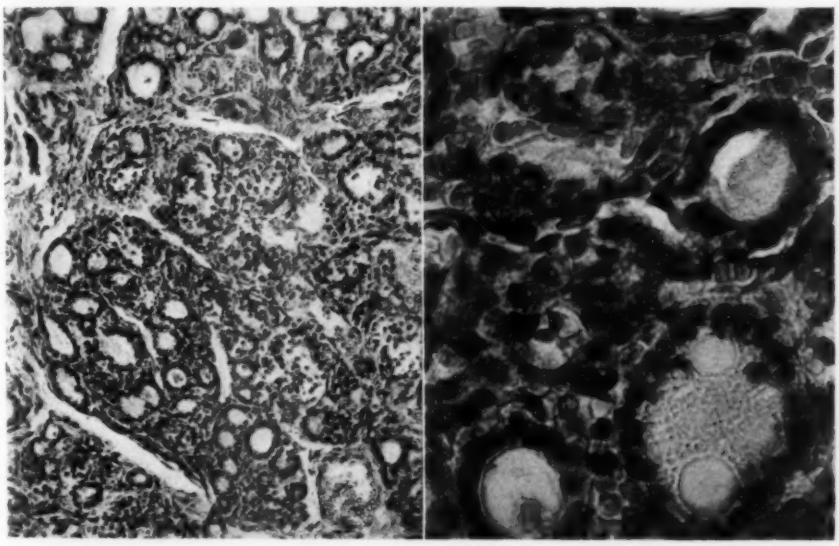

Fig. 1.—Thyroid of a child aged 7 months. *A*, fibrous tissue bundles dividing the area into fields; *B*, well formed acini containing thin colloid. Between are masses of cells showing solid masses or the beginning of acini.

The infantile gland is characterized by heavy columns of fibrous tissue which divide the gland into fields. It appears as though the gland is provided with enough connective tissue to supply it in its adult size. The arrangement of these connective tissue bundles gives the examiner a clue as to why nodular enlargements are found in goiters.

The embryo gland cells form solid masses from which in time the acini develop. In the early stages one finds some areas in which definite acini have formed, while in others solid masses remain. The acini vary much in size and in the nature of the contents (fig. 1). One finds statements in the literature to the effect that in the early glands the epithelium stains badly and is sometimes exfoliated. This impression is due to the difficulty of securing fresh material for examination.

One still occasionally finds statements that some of the acini are empty. It would be surprising if this were true, because an empty cavity elsewhere in the body is unknown. If a fluid-containing sac is deprived of its fluid the walls collapse. I believe it can be confidently stated that if the acinus appears to be empty one of two conditions is present: Either the acinal content is so thin that it refuses the dye, or the colloid has fallen out in the process of preparing the slides. The former is proved by the fact that acinal content which refuses the ordinary dyes accepts special dyes. In the infantile gland, for instance, there are no empty acini if Mallory's aniline blue stain is used. On the other hand, if the same material is hardened in solution of formaldehyde it may show no empty acini, while a neighboring block fixed in Zenker's solution may show many "empty" acini. Furthermore, if one mounts a section fixed in Zenker's solution in the regular way and compares it with a fellow slide which has been shaken or penciled, the latter will show many more empty acini. It is not unusual in slides which show many empty acini to find disks of colloid floating about, which have become detached in the process of staining. Naturally, the acinus from which such a disk has been dislocated is "empty." Furthermore, colloid-embedded sections of the same tissue show no empty acini whatever. Of course one finds vacuoles in many thyroid acini, both normal and diseased. What is in a vacuole no one has stated so far as I know, but it is logical to assume that it is some substance that refuses any stain.

Rice wisely refused to discuss the question as to whether there are interstitial cells but pointed out that sometimes there are such and sometimes not, a perfectly obvious fact. In any gland, in childhood, clumps of cells are found between well formed acini which contain no lumens and consequently no colloid (fig. 2). In well preserved tissue this transition can be easily followed—well developed acini, beginning acini containing a little colloid and clumps of cells showing no lumens.

In older children the proportion of acini to cell clumps increases, but until puberty some clumps remain, the acini are lined with cuboidal epithelium and the colloid is thin.

The gland of the young adult is entirely different. The epithelium of the acini is flat and is for the most part uniform. There may be division into lobules by prominent bundles of connective tissue (fig. 3 *A*). The colloid is homogeneous and stains uniformly with eosin (fig. 3 *B*), coloring it just as it does red blood corpuscles. This normally staining colloid may be taken as the sign of the adult period. For the most part the connective tissue is sparse in the adult and is scarcely perceptible unless stained with specific dyes.

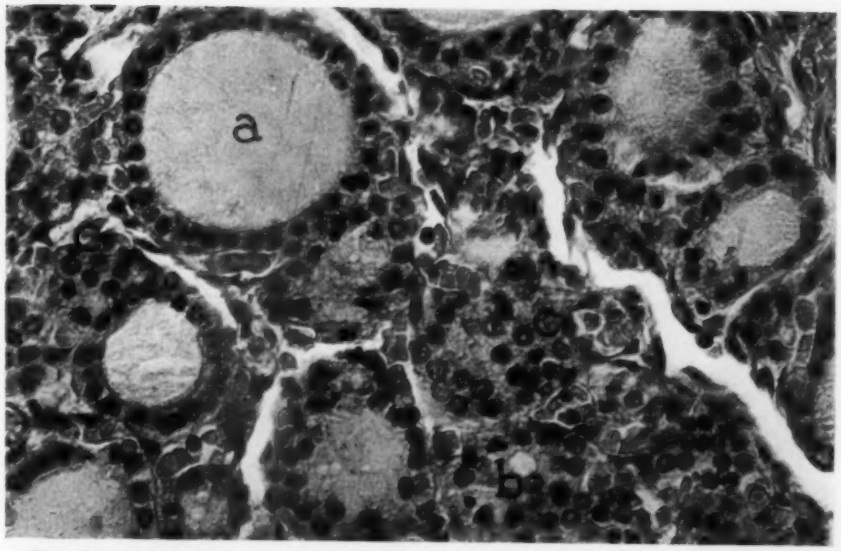

Fig. 2.—Thyroid of a premature child: *a*, well formed acinus containing uniform but palely staining colloid; *b*, very small acinus containing a very little colloid; *c*, clumps of cells without lumens.

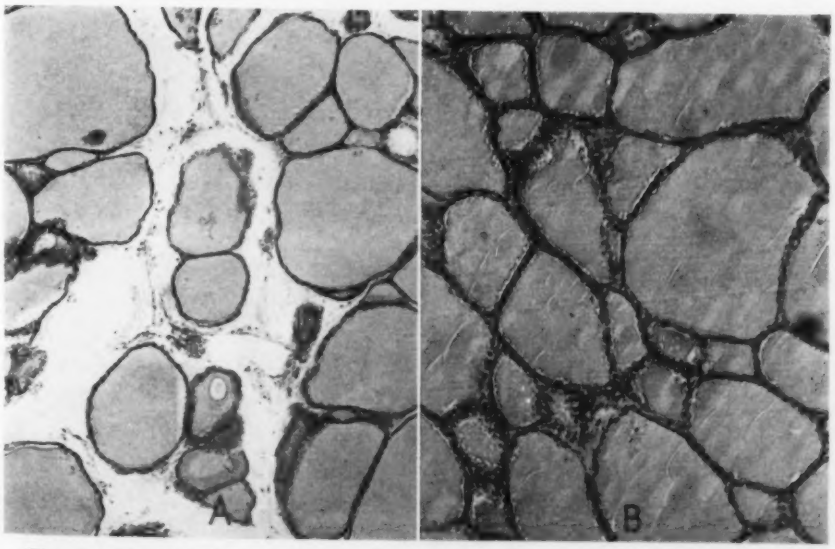

Fig. 3.—Thyroid from a man aged 22. *A*, acini separated by abundant connective tissue. The acini are lined with flat cells and are filled with a uniform colloid. *B*, scattered clumps of cells between the acini.

Many slides show no interacinal cells, but in some specimens such cells are uniformly present throughout the section (fig. 4). Whether these are but vestiges of the infantile stage, as I believe, or have some other significance is at present impossible to say. Patients who have them exhibit some of the nervousness of childhood. On the other hand, some slides of material from patients in early life, even adolescence, show here and there an acinus indicating the degeneration usually found only in mature persons.

In the gland of an aged person, meaning any one beyond the age of 40, the changes encountered are numerous. They involve the connective tissue, the epithelium and particularly the colloid. These may be exam-

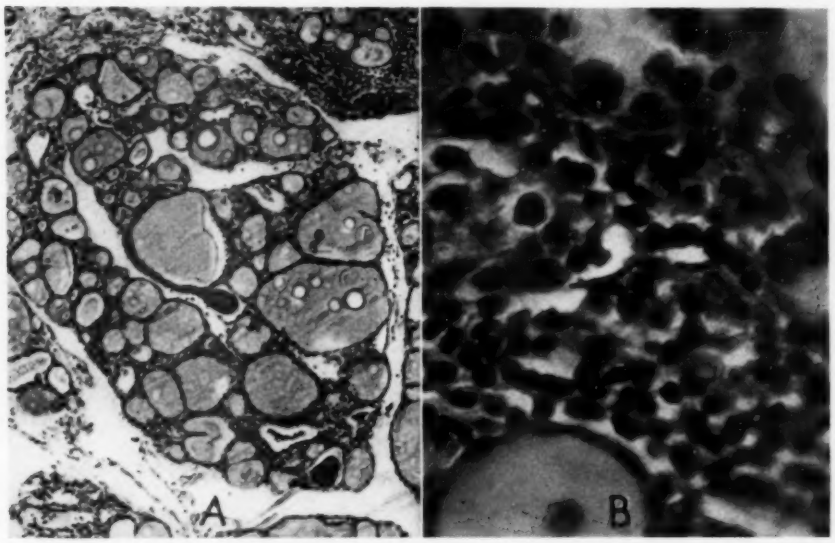

Fig. 4.—Material from a thyroid, showing interacinal cells. *A*, large acini lined with flat epithelium; *B*, interacinal areas filled with a mass of cells without a definite acinus formation (some are lymphoid cells but the larger number resemble those of fetal glands).

ined in turn. It may be stated at the outset that for the most part the changes are frankly regressive.

The constant change of the acinal cells is flattening, even to disappearance (fig. 5 *B*). With this atrophy of the cells, if one may call it such, there is constantly associated a change in the colloid (fig. 5 *A*). This change in the colloid is shown by its refusing the eosin in the usual laboratory stain and accepting the hematoxylin. In other words, it has become basophilic. Before the change can be demonstrated by this simple stain, special stains show it. For instance, the colloid stains orange in Mallory's aniline blue stain before it accepts the hematoxylin.

When this is the case the colloid is always basophilic. The age at which this flattening of the epithelium and change in the colloid occur is not constant. One may find some basic colloid in young persons, but usually it appears only in middle age, and it may be absent even in the aged.

In the aged the acini sometimes tend to reproduce themselves but succeed only in producing small acini with flat cells or in forming clumps of cells without lumens and hence with no evidence of colloid (fig. 6). The function of these newly formed acini, if they are such, is not known. One can say only that in the small acini, which probably represent attempts at reproduction, the cells are irregularly placed, in many filling

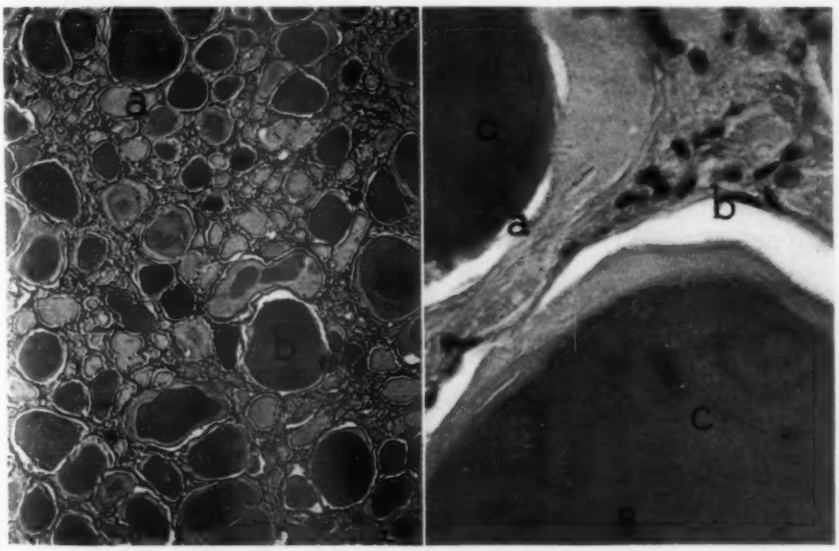

Fig. 5.—Thyroid of an adult. *A*, acini of varying size and staining: *a*, normal colloid; *b*, colloid stained with hematoxylin. *B*, acini with loss of epithelium; *a*, walls of acini without epithelium; *b*, flattened cells; *c, c*, colloid stained with basic stain.

the entire lumen. The structure of these cells seems identical with that of the cells in Hashimoto's struma.

In some cases this aimless attempt at reproduction is even more pronounced. Solid cell masses may give way to cells irregularly placed (fig. 7 *A*). When this irregularity is present and the connective tissue is abundant the condition is sometimes diagnosed as malignant (fig. 7 *B*). These changes are found most commonly in old goitrous glands.

The changes incident to age are better traced in the colloid than in the epithelium. If there are basophilic changes in the colloid one may class the patient as aged whether such changes have been brought about by the passing of the years or by some disease. It is possible that such changes

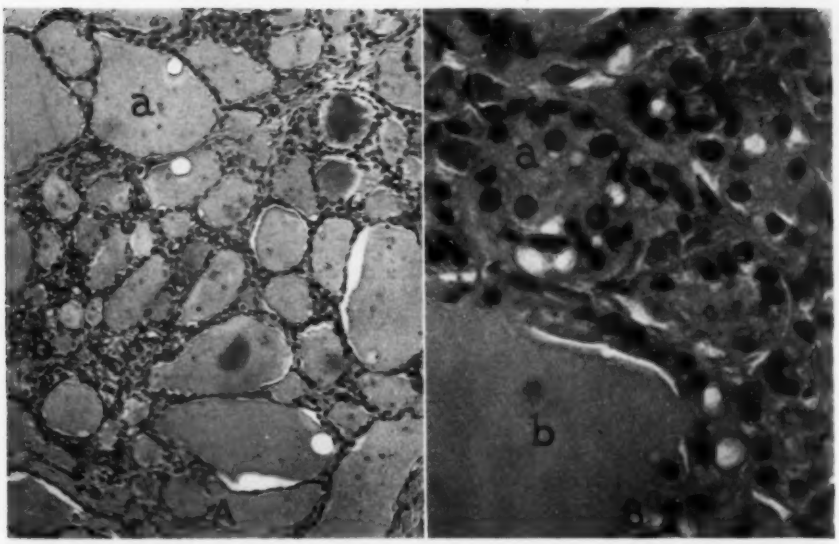

Fig. 6.—Thyroid from M., aged 63: *A*, relatively normal colloid; *a*, acini lined with flat cells; *b*, clumps of cells between the acini. *B*, *a*, cell clumps without lumens; (the cells are granular); *b*, acinus lined with partly defective epithelium.

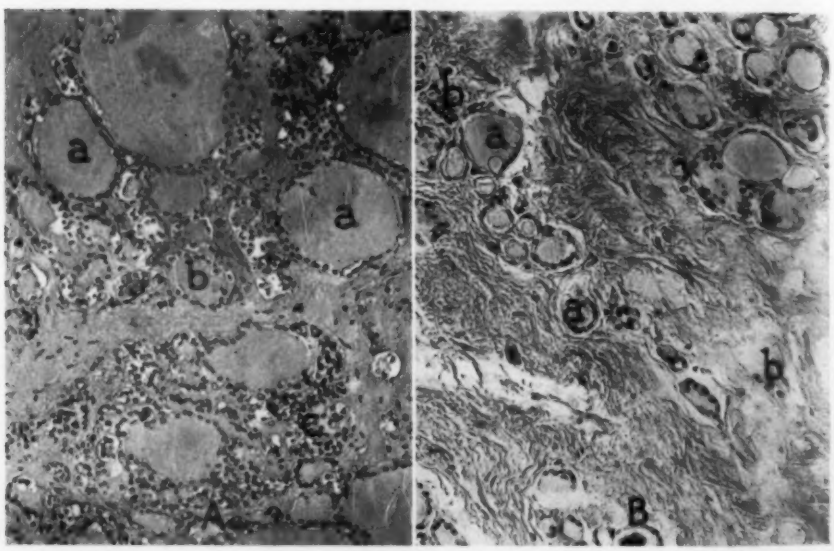

Fig. 7.—Thyroid of a patient aged 56: *A*, *a*, normal acini; *b*, small irregular acini, some with defective walls; *c*, cells diffusely distributed in the connective tissue. *B*, *a*, defective acini; *b*, cells irregularly placed.

are a measure of life expectancy. (Perhaps the insurance companies may ultimately demand an examination of the thyroid before issuing a policy.) These changes can be shown satisfactorily only in colored slides, but even in black and white pictures the differences may be indicated.

In the young adult the colloid stains a uniform deep pink with eosin. On the contrary, the senile gland is characterized by the gradual change in the colloid from acidophilic to basophilic. The cause or meaning of these changes has not been explained.

In the beginning these changes do not show with the usual laboratory stains but are evident with special stains. When senile changes

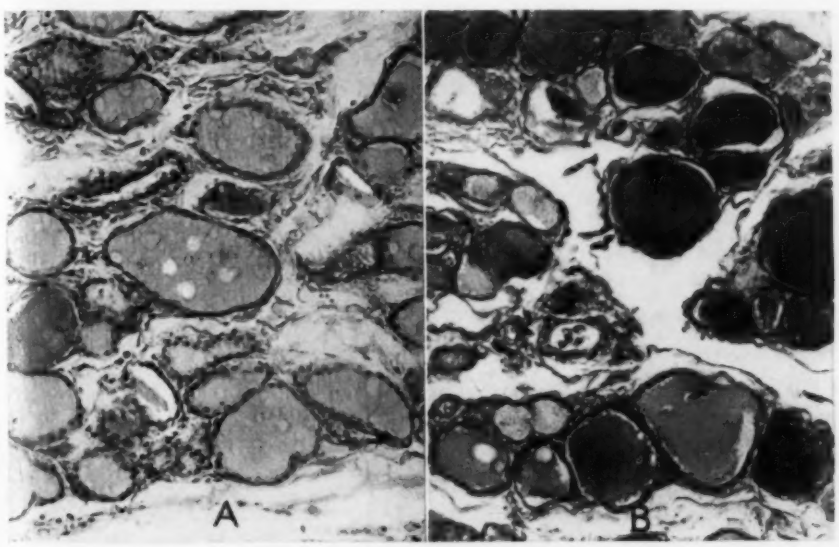

Fig. 8.—Thyroid of a patient aged 42: Biopsy specimen. *A*, hematoxylin-eosin stain. The colloid stains almost normally, with some vacuoles. *B*, tissue stained with Mallory's aniline blue. Many acini show the colloid deeply stained.

occur the colloid no longer stains with eosin but does stain with hematoxylin. With special dyes these changes may be demonstrated much earlier. For instance, the colloid of a gland may stain uniformly with eosin, while if Mallory's aniline blue stain is used some of the acini will take the orange G stain, shown as black in the photomicrograph (fig. 8).

Most slides show all these changes together. It must be repeated that the calendar is not a guide. I recently examined tissue from a man aged 79 which might well have belonged to a man in his prime. As a matter of fact, the thyroid of an aged person is not rarely a well preserved gland comparable with that of early adult life. Perhaps it is

this preservation of the gland that accounts for the fact that some persons become octogenarians.

The acinal cells suffer changes parallel with those in the colloid. Generally speaking, the greater the colloid changes the greater the change in the cells. At best the acinal cells are flat and endothelium-like. In advanced changes in the colloid the cells are absent. Those that are not there most certainly do not function; and since the change from complete absence to the flat cells usually found is so gradual, one is inclined to doubt the functional importance of the thin flat cells lining most of the acini which contain basophilic colloid.

COMMENT

A study of the thyroid glands of supposedly normal persons presents confusing variations. Many show changes parallel with those found in goiters from patients with goiter heart, that is, cardiac disease which disappears after removal of the goiter. Naturally these studies of the nongoitrous gland lead surgeons to ask themselves certain questions. What is the meaning of these changes in chemical reaction of the colloid in allegedly normal thyroids? No one knows, but it is known that these changes are found in goiters from patients with "goiter hearts" and that in such a patient the heart recovers when the goiter is completely removed. So much is incontrovertible. This well demonstrated clinical fact causes one to consider that possibly a degenerated thyroid gland, even though it has not acquired goitrous dimensions, may injure the heart. If this is true, the presence of a "goiter heart" demands the removal of the thyroid gland whether it is goitrous or not. First of all, one must recognize a "goiter heart" by clinical examination. It has been demonstrated to my satisfaction that, in the absence of a palpable goiter, if "goiter heart" is present the removal of the thyroid, enlarged or not, rids the patient of the cardiac disturbance. These observations must be multiplied a thousandfold.

This presents the original question: How big must a thyroid gland be in order to become cardiotoxic? The corollary is, what changes in the thyroid gland must be present before it can be declared the cause of the cardiac symptoms? This is easily decided if one follows the after-course. If the patient recovers from the cardiac signs one may conclude that the part removed was the cause. Multiply such an observation by thousands, and the conclusion is as accurate as one can hope to achieve. The patient, collectively speaking, is always right. If anatomic study does not corroborate clinical experience, one must extend the laboratory study. The surgeon should remember that when he sends a goiter to the laboratory he does so to secure not a diagnosis but an opinion.

This is the problem before surgeons today. Since it is now known that total removal of the thyroid gland from the adult is a matter of indifference to the patient, it becomes merely a question of operative technic.

CONCLUSIONS

The tinctorial as well as the histologic study of the thyroid gland indicates the presence of certain changes which occur with advancing years. These changes parallel to some extent those associated with goiter associated with "goiter heart."

Physicians' knowledge of the relation of the nongoitrous gland to diseases of the heart is at present represented by a large question mark, but even this may presage an advance in understanding of the relation between the nongoitrous and the goitrous gland.

The similarity of structure suggests that the effect of the thyroid gland is a matter not of size but of function. One may determine the nature of this function by removing the gland and observing the results.

INTRACRANIAL HYPERTENSION OF UNKNOWN CAUSE

CEREBRAL EDEMA

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Occasionally one encounters a case which presents clinical symptoms and signs strongly indicative of a tumor of the brain, yet after complete studies one finds no evidence of neoplasm. The condition to be reviewed has been described in the literature under a number of different headings, none of which seems to be satisfactory. Terms such as "serous meningitis," "toxic hydrocephalus" and "pseudotumor" indicate the lack of knowledge regarding the exact nature of this condition.

There are a number of conditions which justly fall into the broad classification of pseudotumor of the brain. Dandy [1] listed and discussed the following: psychoneurosis, encephalitis, Schilder's disease, multiple sclerosis, syphilis, arteriosclerosis, hypertension, sinus thrombosis, various forms of meningitis (tuberculous, fungous and parasitic diseases), cerebral thrombosis and embolism, infantile cerebral palsies, hydrocephalus, macrocephalus, chondrodystrophy, oxycephalus, scaphocephalus and epilepsy.

Dandy classified the cases as those presenting papilledema with increased intracranial tension and those presenting papilledema without increased intracranial tension. He stated further that of all cases in which tumor of the brain is at first suspected, tumor will be subsequently eliminated in fully one-half.

The condition which we report and discuss in this paper is believed by us to be a definite disease syndrome. The patients present strikingly similar clinical and laboratory findings, and it is reasonable to suppose that the underlying pathologic condition in the brain is uniform and consistent in these cases.[2] It is felt that this disease should be

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1. Dandy, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1930, vol. 12, p. 449.

2. We regret that in our cases no material has been subjected to microscopic study, but we hope that opportunities will be afforded in the future for precise clarification of this point.

given consideration as a special entity or as a distinct category of pseudotumor, if from no other than a prognostic standpoint.

It is also believed that many of the cases of pseudotumor presenting papilledema and increased intracranial tension in which the patient progressed to complete recovery with no residual and in which the problem of the pathologic process remained unsolved belong to this group.[3] To such cases various pathologic possibilities have been ascribed but have not been proved to be present. We believe that we have eliminated by ventriculographic study the possibility of localized accumulations of fluid or other localized space-occupying masses. This is based on what one of us (O. H.) accepts as an axiom at the present time: Any localized, space-occupying mass of sufficient size and import to cause an increase in intracranial tension and papilledema will manifest its presence in a pneumoventriculogram.

In connection with the syndrome under discussion, a fairly consistent clinical picture appears in the headache and vomiting in association with papilledema and intracranial hypertension, occurring usually in young persons and terminating as a rule in marked improvement or complete recovery.

To the syndrome represented in this group of cases Quincke[4] in 1897 affixed the diagnosis of "serous meningitis," although other conditions were probably included in his report. The etiologic factors were considered to be influenza, overwork, injury to the head, alcoholism and otitis media.

In 1912, Warrington[5] described this syndrome under the heading of "serous effusions" and concluded that toxins are responsible for the production of excessive amounts of cerebrospinal fluid.

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3. After the reading of a paper by Wilder Penfield (The Principles of Physiology Involved in the Management of Increased Intracranial Pressure, Ann. Surg. **102**:548-554 [Oct.] 1935) the following discussion took place:

Dr. William J. Mixter, Boston: I should like to ask Dr. Penfield why it is that a certain number of patients in the past who presumably had tumor of the brain, though this was never proved, were markedly relieved for a considerable period of time by subtemporal decompressions.

Dr. Wilder Penfield, Montreal, Canada: I find it difficult to answer the question. I think there are a certain number of cases of pseudotumor, which are in reality not cases of tumor at all but cases of collection of subdural fluid, either secondary to trauma or secondary to some primary inflammatory process in one of the sinuses. I think in those instances there is a collection of fluid, high in protein, within the subdural space, which cannot escape. Consequently, decompression allows the fluid to drain into the muscles, and it does not reform, so that in some cases there have been permanent cures from decompression or trepanation.

4. Quincke, H.: Ueber Meningitis serosa und verwandte Zustände, Deutsche Ztschr. f. Nervenh. **9**:149-168, 1897.

5. Warrington, W. B.: Intracranial Serous Effusions of Inflammatory Origin, Quart. J. Med. **7**:93-117 (Jan.) 1914.

Passot [6] concluded that the condition is probably due to excessive cerebrospinal fluid in the subarachnoid space rather than in the ventricles.

Symonds [7] in 1931 reported 3 cases in which the condition followed otitis media and named the condition "otitic hydrocephalus."

Davidoff and Dyke [8] in 1936 reported 15 cases under the heading of "serous meningitis." In this series a history of otitis media was present in 4 cases, and a history of infection elsewhere in the body was obtainable in 2 other instances. The authors commented on the relatively large amount of fluid found in the subarachnoid space or on the "wet" appearance of the brain, as well as on the uniformly good prognosis which attended the condition once a correct diagnosis was made. Pneumoencephalograms taken of all of the patients except 2 showed the ventricles to be normal in size, shape and position. Autopsy on one of the patients, who died from another cause three months after discharge from the hospital, showed no evidence of inflammation of the brain. Questionable edema in the form of pericellular and perivascular spaces was observed.

McAlpine [9] designated the condition in his cases as "toxic hydrocephalus." He reported 5 examples in which nasopharyngeal infection seemed to be the cause.

Bailey [10] stated:

> I believe that these obscure intracranial conditions result, in their chronic form, in the condition called by neurologists chronic serous meningitis and by neurosurgeons chronic arachnoiditis or pseudotumor. The cerebral affection is accompanied by a meningeal inflammation which results in some thickening and interferes with the proper circulation of the cerebrospinal fluid. . . . A sufficient number of necropsy reports exist to prove that such arachnoidal adhesions may be present when there is no tumor and I believe they are secondary to encephalitic affections, the nature of which is at present obscure. The primary disease may have been forgotten or have provoked such slight symptoms as to pass unperceived, while the secondary arachnoidal thickenings by compression of nervous structures or by impeding circulation of cerebrospinal fluid first attract the attention of the physician.

The symptoms of this disorder are those of intracranial hypertension without localizing phenomena. The problem, therefore, becomes identified at once with tumor of the brain in general and tumor of the posterior

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6. Passot, R.: Méningites et états méningés aseptiques d'origine otique, Thesis, Paris, no. 247, 1913.

7. Symonds, C. P.: Otitic Hydrocephalus, Brain **54**:55-71 (April) 1931.

8. Davidoff, L. M., and Dyke, C. G.: A Presentation of a Series of Cases of Serous Meningitis, J. Nerv. & Ment. Dis. **83**:700-705 (Feb.) 1936.

9. McAlpine, D.: Toxic Hydrocephalus, Brain **60**:180-203 (June) 1937.

10. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

fossa in particular. The predominant symptom is headache, the onset of which is relatively acute. Vomiting consistently follows headache if the condition is severe. Occasionally somnolence and diplopia occur. Failure of vision may occur as the condition progresses, owing to choking of the disks. Convulsions occur rarely. Occasionally the patient complains of dizziness and unsteadiness. However, he is usually afebrile and appears surprisingly well in spite of definite signs of increased intracranial pressure. Papilledema is usually present. Ocular palsies, significant changes in the visual fields, nystagmus, ataxia and symptoms referable to the pyramidal tract rarely are present. Our cases have been typical in that there have been no definite localizing signs. The spinal fluid pressure is increased, but the constituents of the fluid are normal.

Pneumoencephalograms are indispensable for the exclusion of tumor of the brain. Once the nature of the condition is established, conservative management in the form of lumbar puncture and dehydration may be indicated. Subtemporal decompression will become the procedure of choice if more conservative measures are not effective in preventing failure of vision.

During the past two years, 5 examples of this disorder have come to our attention. In each case, at the time of the patient's admission to the hospital the tentative diagnosis was tumor of the brain, the history and clinical findings being not sufficiently clear to enable us to make a diagnosis with any great degree of certainty. Ventriculographic study was considered to be necessary before a proper diagnosis could be established and treatment instituted.

The patients ranged in age from 7 to 24 years. Three were females and 2 were males. Four of the patients gave histories of preceding or coincident infection as follows: 1 patient, mastoiditis, 1, cholecystitis and cholelithiasis, and 2, fever of undetermined origin. Complete recovery occurred in 3 patients. One patient had a moderate reduction of vision as a result of postpapillitic atrophy of the optic nerve. In another mild behavior difficulties seemed to be the only residual manifestation. Pneumoencephalograms were taken in each instance—4 ventriculograms and 1 encephalogram, the latter being made after ventriculographic study had been unsuccessful. The ventricular systems in the 5 patients were entirely normal.

REPORT OF CASES

CASE 1.—E. H., a white girl aged 7 years, was referred to the University Hospital by Dr. S. B. Chase, of Fort Dodge, Iowa, in March 1936.

History.—Shortly before Christmas 1935 the patient began to complain of severe headaches extending from the frontal to the occipital region. The head-

aches were frequently associated with nausea and vomiting, the latter being at times projectile, and there were several attacks of vertigo. She lost weight and strength.

About six weeks before examination she complained of severe earache on the right, associated with high fever, and was confined to bed for a week. The ear discharged some pus spontaneously, after which a diagnosis of mastoiditis was made and mastoidectomy was performed. The wound was completely healed eleven days prior to the child's admission to the hospital, but the headache was not relieved.

Other factors were: mild strabismus on one occasion, tinnitus at times, irritability on hearing noises, poor vision and peculiar mental episodes characterized by bizarre questions.

The past history of the patient and the family history were unessential.

Examination.—The child appeared pale and poorly nourished, cried easily and seemed below normal mentally.

The temperature was 98.6 F.; the pulse rate, 98; the respiratory rate, 22; the blood pressure, 100 systolic and 60 diastolic.

The tonsils were large and injected, and there were several large nodes in the right anterior triangle of the neck. The neck was not stiff, but the child complained of pain in the chest on bending the neck. The mastoid scar was well healed, and the ear drums did not appear abnormal.

The pupils and extraocular movements were normal. Vision was 6/8 and 6/10 in the right eye and the left eye, respectively. The visual fields were full. There was bilateral papilledema of 1 diopter, with many hemorrhages.

The child held her head somewhat tilted to the right when walking. The function of the seventh nerve seemed a little more active on the right than on the left. The tongue projected slightly to the right. Alternate movements of the tongue and hands were performed with abnormal slowness.

Laboratory tests showed: hemoglobin, 72 per cent; red blood cells, 3,650,000 per cubic millimeter and white blood cells, 8,350. The blood smear was normal. The Wassermann reaction of the spinal fluid was negative. Urinalysis gave negative results. Spinal puncture revealed a pressure of 200 mm. of water with the patient in the prone position. The fluid contained considerable globulin and 450 cells (bloody tap).

With the diagnosis of increased intracranial tension ("tumor syndrome") of unknown cause, a ventriculogram was taken. Twelve cubic centimeters of fluid was replaced with an equal amount of air. Both lateral ventricles and the third ventricle were well visualized and appeared normal in every respect (fig. 1).

Course.—Her condition changed little during the ensuing three weeks, but the spinal fluid at this time revealed a pressure of 480 mm. of water.

Subsequent to this she made steady improvement, complaining less and less of headache and vomiting only occasionally. After another two weeks the spinal fluid pressure was 170 mm. of water, and the papilledema had almost entirely subsided.

At the final check-up, made eight months after the first admission, the child appeared perfectly well. The fundi looked normal, and the disks did not appear atrophic. The spinal fluid pressure was 160 mm. of water. She was mentally clear and bright and had no complaints.

CASE 2.—G. W., a white boy aged 12, was referred to the University Hospital by Dr. A. Schultz of Fort Dodge, Iowa, in November 1936.

History.—Nine weeks previously this boy had "taken sick" and vomited. There was high fever, as well as some chilliness. He was thought to have "flu."

Although he felt ill, he was not drowsy and preferred to be up, because lying down increased his headache. He vomited a number of times after eating, but the vomiting was not projectile. The illness began with diarrhea, which later was replaced by constipation. Headache was constant and severe—"a pounding in the left parietal region and on top of the head." This was increased by noise and jarring.

About five weeks prior to examination he noticed double vision and also black specks before the eyes. Subsequently the vision became somewhat blurred. For the past four weeks his neck had been so stiff that he could hardly bend it. He had been rather active and not stuporous throughout the illness. The fever subsided about ten days after the onset, and he did not experience double vision at the time of examination. The headache and blurred vision, however, remained.

The family history was unessential.

Fig. 1 (case 1).—Ventriculogram, anteroposterior view.

He was thought to have had scarlet fever in early childhood. Two years prior to examination there had been a slight injury to the head without unconsciousness. A tonsillectomy had been done five months previous to examination.

Examination.—General physical examination gave negative results throughout. The temperature was 98.6 F.; the pulse rate, 95, and the respiratory rate, 30. The blood pressure on admission was 110 systolic and 65 diastolic.

Neurologic examination revealed bilateral papilledema of 3 diopters. The retinal veins were dilated, and a few small hemorrhages were present. Vision was 6/6 in each eye, and the visual fields were normal save for large blind-spots. The extraocular movements were normally performed. Otherwise the neurologic examination gave essentially negative results.

Laboratory tests showed the blood and urine to be normal. The Wassermann reaction was negative. The spinal fluid pressure was 200 mm. of water with the

patient in the prone position and rose rapidly to 325 on compression of both external jugular veins. The fluid showed a trace of globulin, 34 mg. of protein and 78 mg. of sugar per hundred cubic centimeters, and 9 lymphocytes per cubic millimeter.

With the diagnosis of increased intracranial pressure ("tumor syndrome") of unknown cause a ventriculogram was taken. Only 10 cc. of fluid was obtained, this being replaced with an equal amount of air. The ventriculograms showed normal conditions. The ventricular system appeared, perhaps, a little smaller than normal (fig. 2).

Treatment.—Treatment consisted in moderate limitation of fluid intake and daily spinal punctures for twelve days, after which time the pressure was reduced to about 60 mm. of water with the patient in the prone position.

Course.—The choked disks were definitely receding and the headaches abating when the boy was discharged, at the end of one month.

About two weeks after returning home he had a mild recrudescence of the original illness, consisting of a chill and fever associated with intermittent head-

Fig. 2 (case 2).—Ventriculogram, anteroposterior view. The angles of the lateral ventricles are sharp, and the ventricles are small.

ache. His appetite remained good, but he vomited on one occasion. At this time he complained of shooting and stabbing pains in both thighs.

The check-up revealed that the disks had receded to about 1 diopter, though the spinal fluid pressure was 220 mm. of water. He was discharged after a short stay in the hospital, and on a check-up made in June 1937, seven months after his original illness, he was found to be feeling well and was free from headaches. The eyegrounds showed complete recession of the papilledema, with only a slightly fuzzy appearance of the disk margins. A spinal puncture was not made at this time, but it was felt that the patient had made a full recovery.

CASE 3.—E. F., a white boy aged 12, was referred to the University Hospital in November 1936, by Dr. George Stevenson of Cedar Rapids, Iowa.

History.—Six months prior to his admission to the hospital the patient began to complain of severe frontal headache, present day and night and aggravated by walking and jarring. He slept excessively. Two months later he became dizzy,

at which time a physician stated that the temperature was elevated and that the optic disks were choked. Two months before admission he noticed a swelling under the left jaw. This condition seemed to aggravate the headache. Several projectile emeses occurred at this time.

The family history and the past history of the patient were unimportant.

Examination.—The boy appeared lethargic. The temperature was 98.4 F.; the pulse rate, 66 and the respiratory rate, 16. The blood pressure was 108 systolic and 69 diastolic. General physical examination showed normal conditions except for moderate enlargement of the submaxillary lymph nodes.

Neurologic examination revealed that the pupils reacted well to light and came down well on accommodation. Nystagmoid jerks were elicited on deviation of the eyes to the right and left. There was no strabismus. The fundi were

Fig. 3 (case 3).—Ventriculogram, anteroposterior view, taken after spinal injection of air. The defect of the skull is an artefact.

normal. The other cranial nerves were intact. The neck was not stiff. The strength of the extremities, the reflexes and the sensory responses were normal.

Laboratory studies showed a normal blood count and normal urine. The Wassermann and Kahn reactions of the blood were negative. The spinal fluid was under an initial pressure of 24 mm. of mercury (326 mm. of water) with the patient in the prone position. The spinal fluid was clear. The Pandy test for globulin gave a negative result. There was 1 lymphocyte per cubic millimeter. The Wassermann reaction of the spinal fluid was negative.

The tentative diagnosis was tumor of the posterior fossa.

Ventriculographic study was unsuccessful. Encephalograms were satisfactory, revealing an entirely normal ventricular system (fig. 3).

Course.—Improvement was gradual. At examination in March 1937, five months later, the boy was entirely normal.

The final diagnosis was encephalitis.

CASE 4.—J. H., a white woman aged 24, was referred to the University Hospital in January 1937, by Dr. F. E. Simerel of Brooklyn, Iowa.

History.—About four months previous to admission the patient began having headaches. These were more frequent and more severe in the evening, gradually increasing in severity. The headache would commonly start over the eyes and radiate to the occiput. Vomiting occurred only once. Three months prior to admission vision became blurred in the left eye, and there was also double vision. The left eye became almost blind in two months. Vision in the right eye became somewhat blurred also.

Fig. 4 (case 4).—Ventriculogram, anteroposterior view. The apparent vertical elongation of the system is due to the angle at which the x-ray tube was placed with respect to the head.

During the early course of the illness there had been a mild fever, the temperature being from 99 to 100 F., but no chills. At the time the vision first began to blur, the left side of the face swelled, and the left eye became puffy. There were cramps in the neck and back, and the neck was stiff.

This patient had previously been admitted to the University Hospital, July 1935. The history and the results of examination were typical of disease of the gallbladder and the Graham-Cole test revealed a nonfunctioning gallbladder. Cholecystectomy, choledochostomy and appendectomy were done, two stones being removed from the common duct. She was discharged improved on the twenty-ninth postoperative day, the T tube having been removed from the common duct.

She had also been subject to frequent sore throats, and on her return to the hospital in November 1935 the tonsils were removed.

Examination.—The patient was obese; otherwise the general examination showed her to be essentially normal.

The pupils and ocular rotations were normal except that convergence of the right eye was poorly performed. Visual acuity was 6/21 in each eye. Both eyegrounds revealed old choking, with some postpapillitic atrophy and stellate retinitis. Both visual fields were irregularly constricted, and the blindspots were enlarged. Otherwise the neurologic examination gave negative results.

A roentgenogram of the skull revealed nothing unusual.

Laboratory studies of the blood and urine disclosed no abnormality. The Wassermann reaction of the blood was negative. The dextrose tolerance curve was not unusual. The spinal fluid was under a pressure of 170 mm. of water with the patient in the prone position. It rose and fell normally on compression of the jugular veins. The cell content was normal. There was a trace of globulin. The protein content was 46 mg. and the sugar content 86 mg. per hundred cubic centimeters.

A ventriculogram was made, which revealed that the lateral ventricles and the third ventricle were of normal size. The ventricular system was normal in every respect, with good visualization of the third ventricle (fig. 4).

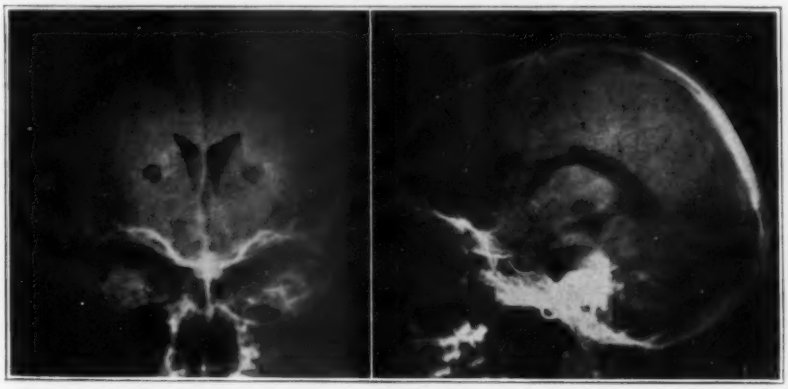

Fig. 5 (case 5).—Ventriculogram, anteroposterior and right lateral views.

Course.—The patient was discharged. Five months later she returned to the hospital. The headaches had gradually lessened until she was almost entirely free from them. She no longer complained of double vision, and the visual acuity had improved, being 6/15 in each eye. The visual fields showed some widening as compared with the findings on the previous admission. The papilledema had almost entirely receded, and there was evidence of moderate postpapillitic atrophy. Otherwise the general and neurologic examinations gave negative results. It was evident that she had made considerable spontaneous improvement.

Case 5.—R. S., a white girl aged 12, was referred to the University Hospital in August 1937, by Dr. J. M. Fettes of Spencer, Iowa.

History.—About two weeks previously, without apparent cause, she had begun to have headache referred to the forehead and behind the eyes. It was present most of the time but worse in the evening. She had vomited several times, the vomiting being projectile. Acetylsalicylic acid gave some relief.

For the past one and a half weeks she had remained in bed. She had been drowsy and had slept most of the time.

Recently the headache had been located in the back of the head. The vision had become blurred, and at the time of examination she "saw double," because of which she kept one eye closed. She complained of ringing in the ears.

The family history and the past history of the patient were unessential except that the patient had had frequent attacks of sore throat.

Examination.—The patient lay on a cart with the eyes closed. She appeared ill and was drowsy but could be aroused without difficulty. The temperature was 100 F.; the pulse rate, 68; the respiratory rate, 18; and the blood pressure, 108 systolic and 70 diastolic. Otherwise the general examination gave essentially negative results.

Neurologic examination gave the following significant findings: The pupils and ocular rotations were normal. Visual acuity was 6/9 in the right eye and 6/18 in the left. The visual fields were moderately constricted and the blind spots enlarged. The eyegrounds revealed papilledema of about 3 diopters. The retinal veins were engorged and tortuous. Audition was normal. The results of caloric tests were normal. The neck was rigid and painful on movement. The Kernig sign was present to a moderate degree on both sides. Alternate movements were performed with abnormal slowness on both sides. When standing with heels together and eyes closed, the girl tended to fall backward. Her gait was slow and careful, and she veered to the right.

Laboratory studies showed the blood and urine to be normal. The Wassermann reaction of the blood was negative. A spinal puncture revealed a spinal fluid pressure of 370 mm. of water with the patient in the prone position. The fluid gave a positive reaction to the test for globulin and contained 1 lymphocyte per cubic millimeter. The Wassermann reaction was negative.

The impression was that of a subtentorial tumor, but a ventriculogram showed the lateral ventricles and the third ventricle to be normal in every respect (fig. 5).

Course.—The patient improved under conservative management, so that two weeks after admission she was mentally alert and cheerful and did not complain of headache. At this time a spinal puncture revealed a pressure of 70 mm. of water, with normal rise and fall when pressure was applied to and released from the jugular veins. The fluid gave a positive reaction to the test for globulin. It contained 38 mg. of protein per hundred cubic centimeters and 15 lymphocytes per cubic millimeter.

The papilledema appeared to be receding. The patient was discharged with a diagnosis of encephalitis.

COMMENT

The cases reported here, while a small series, nevertheless present a clinical syndrome of intracranial pathologic disturbance which has certain definite characteristics. The literature is not devoid of similar case reports.

The important characteristic feature of these cases is the unexplained intracranial hypertension. The history may or may not disclose a concomitant or preceding infection or systemic disease. The condition appears to be largely a disease of youth, the patients coming to the physician because of relentless headache. The signs found on examination can be attributed principally to increased intracranial tension and are characteristically papilledema and high pressure of the spinal fluid.

Outstanding complaints in this series of cases were irritability, somnolence and headache that was made worse by the slightest jarring. Stiffness of the neck was definite in 4 instances.

The protein, sugar and cell contents of the spinal fluid were within normal limits. A trace of globulin was elicited in 2 cases.

From this series it would seem that if there are chills and fever during the course of the illness they are related to the systemic infection rather than to the intracranial condition primarily.

Inasmuch as the patient presents symptoms of a tumor of the brain without localizing signs, a ventriculogram is indispensable to correct diagnosis. The normal ventriculographic picture rules out neoplasm.

One of us (O. H.) has never encountered a tumor of the brain associated with increased intracranial tension that was not also accompanied by evidence of dilatation, distortion or filling defect of the ventricles.

Recovery occurs over a period of several months to a year or so, with no neurologic residuals except postpapillitic atrophy of a degree depending on the severity and duration of choking of the disks.

Whether repeated spinal punctures or artificial dehydration measures hasten recovery is difficult to say. Concerning our cases, in retrospect, we do not believe that surgical decompression would have been of sufficient added advantage to warrant the procedure. The process was undoubtedly subsiding in the patient in case 3 at the time of her admission to the hospital. It was felt that little could have been gained by decompression. It is possible, however, that certain patients will require this procedure because of rapidly advancing visual loss.

In fact, little active treatment of any kind was administered to any of these patients except one. Most of the recovery occurred at home.

A rational rule of therapy might be as follows: The diagnosis having been established and it having been ascertained that the spinal fluid pressure is 250 mm. of water or more with the patient in the prone position, daily spinal punctures and dehydration measures are in order. The papilledema should be carefully followed. If this progresses objectively and there is evidence of diminishing visual acuity in spite of conservative measures, subtemporal decompression may be justified. It is reasonable to expect operative decompression to relieve the patient subjectively and to prevent additional damage to the optic nerves.

As our cases indicate, however, decompression is not always necessary for an excellent outcome.

On the other hand, the symptoms of this disease, unlike those of hydrocephalus, are materially alleviated by subtemporal decompression.

The hypothesis that some interference with the absorption of cerebrospinal fluid is the cause of increased intracranial tension appears to be almost universally accepted.

The one outstanding fact which disproves this idea is the absence of dilatation of the ventricles. In fact, the ventricular system may seem smaller than usual, regardless of when the ventriculogram is made during the course of the illness. This same impression was gained by Davidoff and Dyke.[8]

The one definite fact which has been elicited from the cases here reported is that the disease is not hydrocephalus. Additional cases reported in the literature in which pneumograms were made reveal the same findings. In the light of our understanding of cerebrospinal fluid circulation and obstructive hydrocephalus, any reduction in the absorption of cerebrospinal fluid here could hardly be acceptable.[11] Consequently, any diagnostic term incorporating hydrocephalus would appear to be wrongly applied.

If this assumption is correct—that decreased absorption of cerebrospinal fluid is not the fault—only one other cause can remain, and that is swelling or edema of the brain.

A "wet" brain, with particular reference to increased depth of the subarachnoid spaces, has been described in the literature. On making trephine openings preparatory to ventricular puncture, one of us (O. H.) was not impressed with this condition in the cases reported here, although only a limited area of the cortex was examined. In reviewing his own experience, he does not find that he ever encountered a wet, cystic appearance of the subarachnoid spaces except where some degree of cerebral atrophy had occurred.

Davidoff, however, encountered this condition in 13 of his 15 cases in which surgical decompression was done. It is not unreasonable to suppose that edema of the subarachnoid space might be a part of a generalized extracellular and interstitial edema without interfering materially with normal circulation of the cerebrospinal fluid.

The same evidence that speaks for the improbability of decreased absorption of cerebrospinal fluid as a cause of intracranial hypertension speaks against excessive production of cerebrospinal fluid as a cause.

It is evident in the present group of cases that the pathologic process was not severe enough to cause destruction of brain tissue. The evi-

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11. We have encountered another condition (malignant hypertension) which, when associated with increased intracranial tension is also associated with a normal or smaller than normal ventricular system. A postmortem examination in such a case revealed changes in the cerebral vessels, edema of the white matter and hemorrhage. Evidently the increased tension in this condition is due to cerebral edema and not to obstruction of the circulation of the cerebrospinal fluid.

We have also made encephalograms in a few cases of meningitis (in 1 instance, tuberculous) and have reviewed encephalograms in such cases made by the department of pediatrics. In every instance the ventricles have been dilated and the sharp angles in the ventriculographic shadows rounded. In such cases the increased tension is largely contributed to by interference with absorption of cerebrospinal fluid, as a result of which the ventricles become dilated.

dence of this is the fact that there is no neurologic residual and the fact that the ventriculograms did not indicate atrophic changes. The time which had elapsed between the onset of the disease and the taking of ventriculograms in 4 of the cases was sufficient to have enabled one to demonstrate atrophic changes if the disease had been destructive. The interval between the onset of disease and the ventriculographic examination in each of the five cases was two and one-half months, nine weeks, six months, two and one-half months and two weeks, respectively.

That the white matter can undergo tremendous swelling from a number of causes (tumor, infection, trauma) is common knowledge. Intracellular edema with demonstrable swelling of the oligodendroglia may be an important factor.[12] This type of edema is prolonged and is probably unrelieved directly by spinal fluid drainage.

We believe that this is the pathologic process underlying the syndrome in the cases reported here and that it develops as a reaction to toxins—a sterile process. The fact that it is not an inflammatory process in the true sense is evidenced by the absence of an abnormal number of leukocytes and of increase in the protein of the spinal fluid. The edema is probably evolved in a relatively short period but subsides slowly.

For this particular group of cases, we believe cerebral edema would be a more fitting diagnosis than any which has as yet been proposed.

We believe that it is equally important that this syndrome be not confused with, or diagnosed as, encephalitis. This syndrome differs from encephalitis in three significant ways: 1. Encephalitis is commonly characterized by convulsions. Convulsions have not occurred in this syndrome. 2. In encephalitis the spinal fluid demonstrates cytologic and chemical evidence of inflammation, while in this syndrome the constituents of the fluid are strikingly normal. 3. Encephalitis is commonly followed by neurologic residuals. Ventriculographic evidence of cerebral destruction and atrophy is repeatedly obtainable. The reverse is true of this syndrome.

CONCLUSIONS

1. A syndrome variously referred to as "pseudotumor," "serous meningitis" and "otitic hydrocephalus," 5 cases of which are here reported, is probably due to cerebral edema, extracellular, intracellular or both.

2. Cerebrospinal fluid that appears consistently normal from cytologic and chemical standpoints excludes an inflammatory process of the cerebrum or meninges.

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12. Penfield, W.: A Further Modification of Del Rio Hortega's Method of Staining Oligodendroglia, Am. J. Path. **6**:445-447 (July) 1930. Penfield, W., and Cone, W.: Acute Swelling of Oligodendroglia: A Specific Type of Neuroglia Change, Arch. Neurol. & Psychiat. **16**:131-153 (Aug.) 1926.

3. Absence of the slightest evidence of ventricular dilatation at any time during the disease excludes the possibility that decreased absorption or excessive production of cerebrospinal fluid is the cause of the increased tension. Likewise, this finding demonstrates that cerebral atrophy does not occur and hence that the pathologic process is not destructive (except for the atrophy which may follow prolonged papilledema).

4. For the present, cerebral edema would be the most fitting diagnosis for this type of pseudotumor.

5. Recovery is spontaneous (requiring a period of months) and occurs even when no decompressive therapy is administered.

SWELLING OF THE BRAIN IN CASES OF INJURY TO THE HEAD

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Dehydration methods in the treatment of injury to the head have refocused attention on the subject of the water content of the brain and the partition of fluids within the cranial cavity. The total volume of the cranial content is fixed by the rigid confines of the bony cranial walls (Monroe-Kellie Doctrine).[1] To maintain pressure equilibrium, a change in one component should be associated with a reciprocal change in some other.[2] The components involved are brain tissue, cerebral fluid and blood. The major factor is brain tissue, the chief subdivisions of which are solid matter (which is constant), intercellular water, intracellular water and parenchymatous hemorrhages. The cerebral fluid is divided into the subarachnoid and ventricular parts.[3] The extraparenchymatous blood includes that within the vessels outside the brain as well as that extravasated as subarachnoid, subdural or extradural hemorrhage.[4]

It has long been taught that with trauma to the head there are an increase in quantity of cerebral fluid and a swelling of the brain substance by edema.[5] These increases would induce a corresponding decrease in blood content of the brain and would lead eventually to

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From the Cook County Hospital and from the Department of Physiology, the Northwestern University Medical School.

1. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injections of Various Solutions of Various Concentrations, Am. J. Physiol. **48**:512, 1919. Page, I.: Chemistry of the Brain, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

2. Reichardt, M.: Ueber die Untersuchung des gesunden und kranken Gehirnes mittels der Wage, Jena, Gustav Fischer, 1906.

3. Jackson, H.: The Circulation of the Cerebrospinal Fluid, J. A. M. A. **79**:1394 (Oct. 21) 1922.

4. Jackson, H.: Head Injuries, Practitioner **138**:188, 1937.

5. (*a*) Werden, D. H.: Drainage of Cerebrospinal Fluid in the Treatment of Acute Head Injuries, Arch. Surg. **34**:424 (March) 1937. (*b*) Häussler, G.: Hirndruck—Hirnödem—Hirnschwellung, Zentralbl. f. Neurochir. **2**:247, 1937. (*c*) Wilson, F., and Gorrell, R.: Traumatic Edema with Skull Fracture, Nebraska M. J. **21**:95, 1936. (*d*) Craig, W. M.: Physiology, Pathology and Treatment of Craniocerebral Injuries, New England J. Med. **212**:77, 1935.

serious cerebral anemia.[6] The increased quantity of cerebral fluid has been attributed to irritation by extravasated blood[7] or to decreased absorption. The cerebral edema has been attributed to compression of fluids out of the capillaries, to vasomotor paralysis, to anemia and osmotic changes and to accumulation of acid because of the anemia.[8]

The doctrine of an increased quantity of cerebral fluid after trauma to the head is based partly on the increased cerebrospinal fluid pressure commonly found. An increase in pressure does not necessarily imply an increase in quantity. A swollen brain pressing on the same quantity or even on a smaller quantity of cerebral fluid can produce an increase in pressure. An actual increase in quantity has been attested.[5a] In some cases of head trauma there is no increase in either pressure or quantity of cerebrospinal fluid. While it is conceded that there may be no increase in subarachnoid fluid, other observers emphasize the increase in ventricular fluid.[9] Internal traumatic hydrocephalus is frequently referred to in the foreign literature as an important feature of the surgical pathologic picture presented by head trauma. These considerations have led to the therapeutic principle of lumbar puncture and drainage in cases in which increased cerebrospinal fluid pressure is found.[10] Whether or not the actual quantity of fluid is increased, lumbar puncture will still reduce pressure. The removal of only a small quantity (as little as 14 cc.) may be enough to restore the pressure to normal. To combat the internal hydrocephalus, ventricular drainage has been suggested.[11]

The current tendency, despite considerable disagreement, is to regard the swelling of the cerebral tissue in the absence of gross hemorrhage as the principal compressing factor in head injuries. On the principle that the cerebral swelling is a cerebral edema, an increase in intra-

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6. Lehman, E., and Parker, W.: The Unsolved Problems of Brain Injury, Internat. Clin. **3**:181, 1935.

7. Weed, L. H.: Forces Concerned in Absorption of Cerebrospinal Fluid, Am. J. Physiol. **114**:40, 1935.

8. Pilcher, C.: Experimental Cerebral Trauma: The Fluid Content of the Brain After Trauma of the Head, Arch. Surg. **35**:512 (Sept.) 1937. Jorns, G.: Hirnödem und Hirnschwellung, Chirurg **8**:437, 1936.

9. Arnand, M.: Recherches sur les hypertension intracraniennes bloquées du liquide céphalo-rachidien consécutives aux traumatismes craniens, et en particulier sur les hypertensions intraventriculaires, Bull. et mém. Soc. nat. de chir. **59**:843, 1933. Hauptmann: Die Objektivierung postcommotioneller Beschwerden durch das Encephalogram, Zentralbl. f. d. ges. Neurol. u. Psychiat. **48**:846, 1927.

10. Munro, D.: The Therapeutic Value of Lumbar Puncture in the Treatment of Cranial and Intracranial Injury, Boston M. & S. J. **193**:1187, 1925. Jackson, H.: The Management of Acute Cranial Injuries by the Early Exact Determination of Intracranial Pressure and Its Relief by Lumbar Drainage, Surg., Gynec. & Obst. **34**:494, 1922.

11. Denis, R.: Au sujet du traitement des lésions traumatiques cranio-encéphaliques, J. de chir. **42**:873, 1933.

parenchymatous fluid, dehydration methods have been widely used in treating such injuries.[12] By restricting fluid intake and inducing catharsis, Fay sought to decrease the production of cerebrospinal fluid and to diminish the water content of the brain tissue.[13] The intravenous injection of hypertonic dextrose also extracted water from the tissues.[14] It was found, however, that after producing a brief salutary effect part of the dextrose migrated into the tissues.[15] The dextrose in the blood stream was excreted. The osmotic relation was reversed. Water flowed back into all the tissues, including the brain. The cerebrospinal fluid pressure suffered a secondary rise, and, in addition, shock was favored by reduction in general blood volume.[16] Sucrose solutions administered intravenously have apparently corrected these difficulties because the sucrose molecule does not migrate into the tissues.[17] It has been established clinically and experimentally that a general dehydration diuresis occurs, and there is a fall in cerebrospinal fluid pressure, with no secondary rise and no vascular shock. Occasional reports of nephritis following injections of sucrose and the possible harmful effects of too rapid or too violent dehydration of brain tissue discourage the unrestricted use of this agent.[18]

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12. Weed, L. H., and Hughson, W.: Systemic Effects of the Intravenous Injection of Solutions of Various Concentrations, with Special Reference to the Cerebro-Spinal Fluid, Am. J. Physiol. **58**:53, 1921.

13. Fay, T.: The Treatment of Acute and Chronic Cases of Cerebral Trauma by Methods of Dehydration, Ann. Surg. **101**:76, 1935.

14. Sachs, E.: Treatment of Head Injuries, Internat. J. Med. & Surg. **46**: 567, 1933; The Diagnosis and Treatment of Head Injuries, J. A. M. A. **81**:2159 (Dec. 29) 1923. Jackson, H.; Kutsunai, T.; Leader, L. O., and Joseph, L. D.: Effect of Hypertonic Dextrose Solutions on Intracranial Pressure in Acute Cranial Injuries, ibid. **100**:731 (March 11) 1933.

15. Gregersen, M., and Wright, L.: The Effect of Intravenous Injection of Sucrose and Glucose upon the Reducing Power of Cerebro-Spinal Fluid, Before and After Hydrolysis, Am. J. Physiol. **112**:97, 1935.

16. Milles, G., and Hurwitz, P.: Effect of Hypertonic Solutions on the Cerebrospinal Fluid Pressure, with Special Reference to Secondary Rise and Toxicity, Arch. Surg. **24**:591 (April) 1932.

17. Hahn, E. V.; Ramsey, F. B., and Kohlstaedt, K. G.: Clinical Experience in the Use of Sucrose Instead of Dextrose in the Osmotic Therapy of Increased Intracranial Pressure Occurring in Cases of Acute Brain Injury, J. A. M. A. **108**: 773 (March 6) 1937. Jackson, H.; Dickerson, D., and Gunther, A.: The Reduction of Intracranial Pressure in Cerebral Injury by the Intravenous Use of Hypertonic Sucrose Solutions, Ann. Surg. **106**:161, 1937. Bullock, L.; Gregersen, M., and Kinney, R.: The Use of Hypertonic Sucrose Solution Intravenously to Reduce Cerebro-Spinal Fluid Pressure Without a Secondary Rise, Am. J. Physiol. **112**: 82, 1935.

18. Masserman, J.: Intracranial Hydrodynamics: Central Nervous System Shock and Edema Following Rapid Fluid Decompression of the Ventriculo-Subarachnoid Spaces, J. Nerv. & Ment. Dis. **80**:138, 1934. Russell, W. R.: Cerebral Involvement in Head Injury, Brain **55**:549, 1932. Barker, H.: Dangers of Rapid Diuresis, Illinois M. J. **72**:313, 1937.

That the brain in the presence of trauma to the head is enlarged and swollen cannot be questioned.[19] The brain in such a condition, according to the estimate of the coroner's physician, Dr. J. Kearns, averages 30 to 50 Gm. more in weight than the normal brain of a person of the same age and weight. That the cerebrospinal fluid pressure is often increased in cases of trauma to the head is undenied. Clinical studies, however, leave many undecided factors, such as the quantity and distribution of the cerebrospinal fluid and the nature of the swelling of the brain. These unknown factors hamper analysis. The following studies were undertaken in order to determine by actual measurement at the autopsy table just how much fluid there is in and about the brain in cases of head trauma and to trace, if possible, the mechanism of the cerebral enlargement. It is recognized that this material represents only end stages in the traumatic process. Yet *mortui vivos docent.* From these end stages physicians should be able to look backward and learn something definite about the pathogenesis of intracranial compression or at least clear the way for more detailed analysis of the mechanisms involved by the more easily controlled experimental method.

There are but few autopsic reports in sufficient detail to permit analysis of the mechanism of swelling of the brain.[20] Small sample methods of determining the water content of the traumatized brain [21] are open to the serious objection that minute variations in the proportions of gray and white matter in the specimens will give greater differences in total water content of the samples than will the trauma itself.[8] Gray matter contains 12 per cent more water than does white matter. In the whole brain there is 57 per cent gray matter and 43 per cent white. Small (10 to 15 Gm.) samples taken from the same area of the brain but differing slightly in the proportion of gray and white matter were found to vary up to 4 per cent in water content. The report, therefore, based on this method, that the brain of a traumatized head contains from 0 to 2.2 per cent more water than does the normal brain cannot be accepted without reservation.[8]

OBSERVATIONS

The amount of cerebrospinal or extraparenchymatous fluid was first determined. In normal brains the total amount of fluid which could be collected at autopsy varied between 30 and 60 cc. This

19. LeCount, E. R., and Apfelbach, C. W.: Pathologic Anatomy of Traumatic Fractures of the Cranial Bones and Concomitant Brain Injuries, J. A. M. A. **74:** 501 (Feb. 21) 1920.

20. Courtney, J. W.: Traumatic Cerebral Edema, Boston M. & S. J. **140:** 345, 1899. Reichardt, M.: Bericht über Folgen der Hernverletzungen, Berl. klin. Wchnschr. **55:**822, 1918. LeCount and Apfelbach.[19]

21. Apfelbach, C. W.: Traumatic Fractures of the Cranial Bones: I. Edema of the Brain; II. Bruises of the Brain, Arch. Surg. **4:**434 (March) 1922.

included the fluid in the subarachnoid spaces of the brain and spinal cord as well as the few cubic centimeters which was found at the bottom of the otherwise empty ventricles. This quantity is less than the 100 to 150 cc. usually given as the normal quantity during life. There may be some agonal or postmortem absorption of fluid, but this factor would probably hold for the definitive as well as the control cases and, in fact, did not vary appreciably with the interval before autopsy, with the terminal temperature or with the cause of death. In patients with alcoholic "wet brain" or in those who died of congestive heart failure or renal failure there was an abundance of cerebrospinal fluid at autopsy (up to 150 to 160 cc.). The sulci were rounded and atrophied.[22]

The brains of traumatized heads showed a disappointing meagerness of fluid in the subarachnoid spaces. In fatal cases we had expected to observe an increased quantity of fluid. Actually, we observed at the autopsy table hardly enough fluid to measure. While there were some exceptions, 5, 10 or 15 cc. was usually as much as could be collected. This was observed mostly in the basal cisterns and in the spinal subarachnoid spaces. Often the cerebral subarachnoid spaces were so dry that there was not even the few drops necessary to maintain the normal luster of the pia mater. The dryness of the subarachnoid spaces after trauma to the head has been described by LeCount. The sulci of the brain were obliterated and the convolutions flattened.

The lateral ventricles, however, were dilated to almost twice the normal size. They were filled with 30 to 60 cc. of fluid which did not run freely into the subarachnoid spaces when the brains were removed. This internal traumatic hydrocephalus has been frequently described, especially in the French literature. It could have squeezed the subarachnoid spaces dry. It could account at least in part for the enlargement of the brain.

To hunt further for the cause of the increased weight of the brain in cases of trauma to the head, the intraparenchymatous water content of a group of brains from traumatized heads and of a group of normal brains was determined by dehydration to a dry residue of constant weight. Large samples, comprising roughly an entire cerebral hemisphere and weighing over 400 Gm., were used. This eliminated the error inherent in the small whole sample method or the error in an insufficiently skilful separation of gray and white matter. Several methods of dehydration were used.

In calcium chloride or sulfuric acid desiccators the normal brain was reduced to constant weight in six weeks and showed a water

22. Roberson, R. S.: Cerebral Edema in Chronic Alcoholism (Alcholic Wet Brain), South. Med. & Surg. **94**:584, 1932.

content of 78.1 per cent.[23] The "alcoholic," or "wet," brain was truly wet, showing after six weeks a water content of 81.6 per cent.[24] The brains from traumatized heads retained water more tenaciously, being finally reduced to constant weight only after three months, and then showed a water loss less than that of the alcoholic wet brain and even less than that of the normal brain. The loss of water from the 3 brains from traumatized heads was 75.7, 75.1 and 74.2 per cent respectively (table 1). These brains were thus even dryer than normal.[25]

It cannot be stated that at the end of the experiment the brain substance was completely dehyrated by this method. Complete dehydration is interfered with by the fat content of the brain. The brain substance was reduced to apparently dry but resin-like small particles which may

TABLE 1.—*Dehydration of Brain Substance by Calcium Chloride Desiccator*

Case No.	Condition of Brain	Hours After Death	Patient: Age	Patient: Weight, Lb.	Patient: Height	Subarachnoid Fluid, Cc.	Ventricular Fluid, Cc.	Weight of Brain, Gm.	Survival After Admission	Terminal Temperature, F.	Treatment	Percentage of Water in Brain
1	Trauma	15	38	150 (68 Kg.)	5′ 8″	10	50	1,536	2 days	104.8	200 cc. 50% sucrose; lumbar puncture	75.7
2	Trauma	8	43	150 (68 Kg.)	5′10″	15	35	1,270	2 days	104.0	200 cc. 50% sucrose; lumbar puncture	75.1
3	Trauma	12	43	220 (99.8 Kg.)	5′ 6″	10	55	1,230	3 hrs.	98.0	None	74.2
4	Normal	8	37	250 (113.4 Kg.)	5′11″	50	6	1,400	3 hrs.	99.6	None	78.1
5	Alcoholic	8	50	140 (63.5 Kg.)	5′ 6″	130	10	1,435	10 hrs.	103.6	200 cc. 25% dextrose	81.6

have retained some water. The method, however, was the same for the control brains as for those from traumatized heads, and all were reduced to constant weight. In subsequent experiments the fat content of the brains was determined. Differences were found, but no correlation could be seen between fat content and water retention. The residue of the normal brain yielded 45 per cent of fat, that of the alco-

23. Skelton, H.: Storage of Water by the Various Tissues of the Body, Arch. Int. Med. **40**:140 (Aug.) 1927. Broemser, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1929, p. 64.

24. Nuzum, F., and Le Count, E.: The Ability of Brain Tissue to Take Up Water in Delirium Tremens and Other Conditions, J. A. M. A. **67**:1822 (Dec. 16) 1916.

25. Sauerbruch, F.: Entwicklung und Stand der Hirndrucklehre, Zentralbl. f. Chir. **64**:703, 1937.

holic brain 56 per cent and that of the traumatic specimens 58, 49 and 59 per cent. No correlation could be found with the age, weight or height of the patient.

The deficiency in water content was thought to be an agonal or postmortem phenomenon, yet this would probably apply equally to the normal and to the alcoholic brains. It was thought that the terminal high temperature in cases of head trauma might have induced a preagonal water fixation or a postmortem water loss. Two of the patients with injured heads had terminal temperatures of 104 and 104.8 F., but the third, with identical loss of water, had a temperature of 98 F.

The patient with alcoholism, with abundant fluid, also had a terminal temperature of 103.6 F.

The brains from traumatized heads were heavier than normal yet gave up less water and gave up what they did yield with more difficulty. One possible explanation is that in trauma to the head there is a shift of parenchymatous fluid from an intercellular to an intracellular position.[26] The water-binding power of the cells, *Wasserverbindungsvermoege,* increases, and the water cannot be broken off even by the method of chemical dehydration used. Morphologically there is no satisfactory method of demonstrating this intracellular fluid. It is difficult to see where the dry, hard, lumpy material which is left after dehydration could hide extra water. It is possible, however, and other dehydration methods were tried in an effort to blast off more water without changing the general results. While it is admitted that some water may still be hidden unreleasably, a second explanation for the discrepancy between increased weight of the brain and decreased yield of water was offered by Dr. R. Vaughan, in the possibility that the extra weight is accounted for by innumerable petechial hemorrhages scattered into the brain substance.[27] These can be demonstrated microscopically (illustration), and added together may account for the increase in weight.[28] At the suggestion of Dr. A. C. Ivy, this was checked by determining the iron content of a second group of brains studied in a similar manner.

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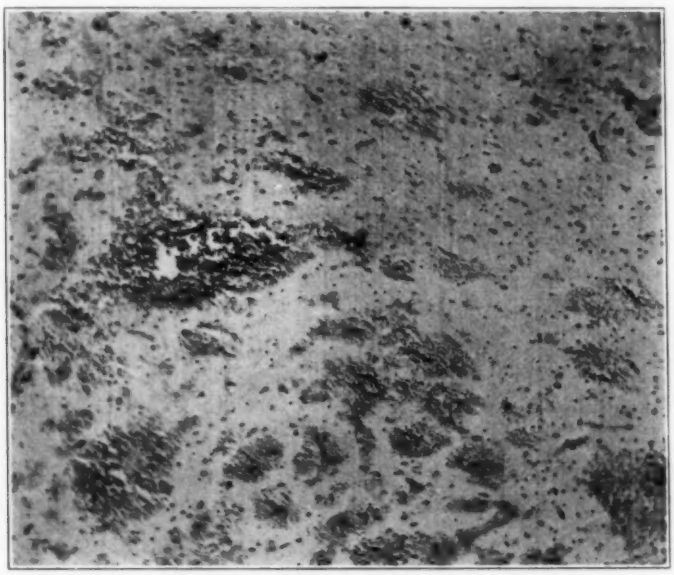
26. Jones, I., and Gortner, R.: Free and Bound Water in Cells, J. Phys. Chem. **36**:367, 1932. Gamble, J. L.: Epilepsy: Evidences of Body Fluid Volume Disturbance, Arch. Neurol. & Psychiat. **23**:915 (May) 1930.

27. Winkelman, N. W., and Eckel, J. L.: Brain Trauma: Histopathology During Early Stages, Arch. Neurol. & Psychiat. **31**:956 (May) 1934. Cassasa, C.: Multiple Traumatic Cerebral Hemorrhages, Proc. New York Path. Soc. **24**:101, 1924. Martland, H. S., and Beling, C. C.: Traumatic Cerebral Hemorrhage, Arch. Neurol. & Psychiat. **22**:1001 (Nov.) 1929.

28. Schaller, W. F.; Tamaki, K., and Newman, H. W.: The Nature and Significance of Multiple Petechial Hemorrhages Associated with Trauma of the Brain, Arch. Neurol. & Psychiat. **37**:1048 (May) 1937. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, ibid. **32**:257 (Aug.) 1934.

In this group the brains were dehydrated by heat in a constant temperature oven at 80 C. Higher temperatures were not used because of errors which might be induced by volatilization of some of the fats. Even at 80 C., some break-up of fat probably occurred. While the losses from dehydration were somewhat greater in this group than in the first, we feel that this may be partly due to fat loss and that the heat method is not quite as trustworthy as the chemical methods. The results, however, with 1 exception, were relatively similar to those obtained by the previous method. The normal brain yielded 79.5 per cent of water, and the alcoholic brain 82 per cent. Two of the brains from traumatized heads yielded 78.4 and 77.7 per cent of water respectively. The third specimen was the only one which yielded an abundance of cerebrospinal fluid. In this brain the sulci were widened and the convolutions flattened. There were cerebral lacerations, with a considerable amount of blood mixed in the subarachnoid spaces. This brain yielded 81.2 per cent of water. The patient from whom this specimen had been taken differed from the other patients with trauma to the head in two respects which may account for the difference in result: He had been given 400 cc. of 25 per cent dextrose intravenously; the secondary osmotic shift of dextrose may have been responsible for pouring fluid back into the brain and into the subarachnoid spaces. Further, on looking up his old records at the Cook County Hospital it was found that the patient had been hospitalized for



Multiple petechial hemorrhages scattered through the brain substance.

three bouts of delirium tremens during the last six months before his final admission with an injury to the head. The alcoholism alone might account for the extra fluid. In this group of brains also, 1 of the patients with a "dry" brain had a terminal temperature of 103 F. while the other had a temperature of 100 F. Both patients with alcoholism had high terminal temperatures. The differences in water content of the brain cannot, therefore, be explained by terminal temperatures.

The brain residues in this group were ashed in a muffle furnace at 600 C. Total ash weights could not be determined, because calcium carbonate is added to the material during the ashing process in order to prevent loss of iron. The method of Farrar [29] was used to determine the iron content. With the amount of iron determined, its equivalent in

TABLE 2.—*Dehydration of Brain Substance by Heat*

Case No.	Condition	Hours After Death	Patient			Subarachnoid Fluid, Cc.	Ventricular Fluid, Cc.	Weight of Brain, Gm.	Terminal Temperature, F.	Survival After Admission	Treatment	Percentage of Water in Brain	Blood in Brain Substance, Cc. per 100 Gm.	Percentage of Fat in Residue
			Age	Weight, Lb.	Height									
6	Trauma	7	47	170 (77.1 Kg.)	5′10″	8	30	1,450	103.4	20 hr.	200 cc. 50% sucrose; lumbar puncture	78.4	32.5	58
7	Trauma	18	38	165 (74.8 Kg.)	5′ 8″	10	50	1,535	100.0	6 hr.	None	77.7	37.1	49
8	Normal	6	50	160 (72.6 Kg.)	5′ 9″	54	6	1,430	99.4	1 hr.	None	79.5	33.4	45
9	Alcoholism	4	46	155 (70.3 Kg.)	5′ 8″	150	12	1,090	102.0	2 hr.	None	82.0	31.5	56
10	Trauma; alcoholism	4	54	145 (65.8 Kg.)	5′ 4″	110	25	1,190	107.0	2 days	400 cc. 25% dextrose; lumbar puncture	81.0	33.4	59

blood was calculated. One gram of ox hemoglobin contains 3.4 mg. of iron (the figure for ox hemoglobin is the one usually employed). At a hemoglobin level of 100 per cent there is 15.8 Gm. of hemoglobin per hundred cubic centimeters of blood in males and 13.8 in females. (All the patients in this series were men.) One hundred cubic centimeters of male blood is therefore represented by 53.7 mg. of iron, and the same amount of female blood by 46.9 mg. of iron.

29. Farrar, G.: Determination of Iron in Biologic Materials, J. Biol. Chem. **110**:685, 1935. The ash is dissolved in hydrochloric acid and evaporated to dryness on a steam bath. To the residue, dilute hydrochloric acid is added, with enough water to make up 100 cc. To a 5 cc. portion of this, 2 cc. of hydrochloric acid is added and heated to boiling. One drop of concentrated nitric acid is added to oxidize the iron to the ferric form. Water is added to make up a volume of 25 cc. To this 5 cc. of 20 per cent potassium sulfocyanate and 5 cc. of isoamyl alcohol are added. The reddish color which appears and is extracted by the alcohol is compared with a standard of 0.01 mg. of iron treated in the same way.

By these calculations from determinations of the iron content the normal brain was found to have 33.4 cc. of blood per hundred grams of brain substance, the alcoholic brain 31.5 cc., and the 2 brains from heads with simple trauma 35.2 and 37.1 respectively. This would represent the blood in the vessels plus the blood extravasated in multiple minute hemorrhages. It does not represent gross hemorrhage, as grossly hemorrhagic areas were avoided in taking the samples. With a standard brain weight of 1,400 Gm. these differences would mean that the brains yielding an average of 2.7 cc. of blood more per hundred grams of brain substance would contain 37.8 cc. more of blood altogether. This alone could account for most of the difference in weight between brains from traumatized heads and normal brains.

The alcoholic brain could be estimated to average 26.6 cc. of blood less than the normal brain. The alcoholic brain yielded 33.4 cc. of blood

TABLE 3.—*Dehydration of Brain Substance by Preliminary Acetone Extraction*

Case No.	Conditon	Hours After Death	Patient			Subarachnoid Fluid, Cc.	Ventricular Fluid, Cc.	Weight of Brain, Gm.	Survival After Admission	Terminal Temperature, F.	Percentage of Water		Blood in Brain Substance, Cc. per Gm.	
			Age	Weight, Lb.	Height						Gray Matter	White Matter	Gray Matter	White Matter
11	Normal	6	38	186 (84.4 Kg.)	5'4"	60	8	1,245	3 wk.	102.6	80.47	68.55	36.16	28.1
12	Trauma	10	45	168 (76.2 Kg.)	5'8"	12	45	1,530	2 days	103.0	77.14	65.06	39.09	29.28
13	Trauma	11	40	150 (68 Kg.)	5'6"	6	35	1,420	2 days	102.4	77.89	66.07		

per hundred grams of brain substance, i. e., exactly the same as the normal brain. Whether this is experimental variation or means that the effects of alcohol and trauma neutralized each other is uncertain.

In the light of Pilcher's recent work [8] a third group of brains was studied to determine the effect of head trauma on gray and white matter separately. A third and more rapid method of dehydration was used to meet the possible objection that the slow methods permit oxidation of fat. Gray and white matter were separated. Each sample was extracted with acetone. The residue was placed in a desiccator, and the acetone fraction was dried in an oven at 60 C. The results were relatively the same. In both the normal brains and brains from injured heads, gray matter contained about 12 per cent more water than did white matter. Gray matter also contained more blood. In the brains from injured heads the gray and white matter each contained about 3 per cent less water than did the corresponding parts of the normal brains, and each contained more blood. The gray and the white matter are affected by trauma in

about the same way. Pilcher in his experimental work could find no conclusive evidence of any noticeable post-traumatic cerebral edema. He suggested that intracranial blood volume is of greater importance than cerebral edema in increasing intracranial pressure after trauma.

COMMENT

The findings for absolute water content depend somewhat on the method of dehydration. All heat methods are open to the error introduced by volatilization of fat, and this would tend to increase the figures for water content. Slow oxidation of fat, on the other hand, tends to decrease the value for water yield. For purposes of comparison a uniform method must be used. Within the limits of each method, however, the observations were remarkably constant. It may be that during life these conditions do not obtain, but certainly one can state that after death the brain of a traumatized head is not edematous but dry. Subarachnoid fluid is not increased but decreased. The ventricular component, however, is increased. The brain does not contain less blood than normal, but more.

In the traumatized head the brain is accordingly swollen but not edematous; the swelling is not due to increased water but to increased blood content. How much of the blood in a traumatized brain is inside the vessels and how much is functionless, extravasated blood was not determined in these studies. The brain may have more blood within it yet may suffer functional cerebral anemia. Separation of the two factors is extremely difficult in autopsic specimens. It would have been possible to wash out the intravascular blood first by perfusion. Determinations of iron after perfusion would have given the quantity of extravasated blood alone. The intravascular component could then be determined by estimations of the iron content of the perfusion fluid. Perfusion would have spoiled the determinations of water content and has therefore not yet been done. It will be applied, however, in the experimental approach which is now in progress, so that these two factors will be separated. Even when the analysis is carried to the point of splitting off the extravascular blood component, the question of intravascular functional blood in brain of a traumatized head will not be settled. Quantity of blood is not synonymous with function of blood. Changes in general flow velocity within the brain and especially differential changes in velocity of flow in the various elements of the vascular tree within the brain will have to be determined before the functional factor of blood is understood. In the meantime it might still be possible to establish an increased quantity of specifically intravascular blood in the brain of a traumatized head and still have, for instance through precapillary stasis, a functional cerebral anemia.

While the differences in blood content are significant, the actual figures obtained for blood content as calculated by the iron determination method cannot be accepted at face value because the nonhematic iron of brain substance is included in these determinations along with the hematic intravascular iron. The nonhematic iron of the brain varies with the portion of brain studied and with the age of the patient.[30] The large sample method used in our studies and the fact that our patients were all in the same age group make the differences reliable. We cannot determine the actual hematic iron fraction in our studies by subtracting a known nonhematic iron constant, because although many determinations of the iron content of normal and pathologic brains have been made, the reports do not specify whether the material was first cleared of hematic iron by perfusion.[31] The direct determination of the circulating blood content of the brain by the collargol method [32] is the only feasible approach. This, however, requires experiments in vivo and cannot be done on autopsic material. The difference between this estimate and the total iron content of the brain will give the nonhematic iron constant. How the collargol method will apply to the extravasated blood fraction in the presence of trauma remains to be seen, but the results will probably be irregular.

There was no constant correlation between the autopsic observations and the period of survival after admission to the hospital. In 4 cases of trauma the time of the accident was not known. The known period of survival varied from three hours to two days. Autopsy was done between three hours and eighteen hours from the time of death. No significant difference was attributable to this variation.

The 3 patients with injured heads who lived for more than a few hours had been given 50 per cent sucrose intravenously and one or two lumbar punctures. One patient who lived for two days and 3 who lived for only a few hours were given neither treatment. In this small series we could find no significant differences in the autopsic observations for the two groups. All had about the same dryness of the subarachnoid spaces and brain tissue, about the same ventricular distention and the same somewhat more variable increase of blood content. It may be that at death many differences are canceled. It may be that when the

30. Weil, A.: Vergleichende Studien über den Gehalt verschiedener Nervenbestandteile an Asche, Ztschr. f. physiol. Chem. **89**:349, 1914.

31. Alexander, L., and Myerson, A.: Minerals in Normal and in Pathologic Brain Tissue, Studied by Micro-Incineration and Spectroscopy, Arch. Neurol. & Psychiat. **39**:131 (Jan.) 1938.

32. Weil, A.; Zeiss, F., and Cleveland, D.: The Determination of the Amount of Blood in the Central Nervous System After Injection of Hypertonic Solutions, Am. J. Physiol. **98**:363, 1931.

traumatized brain with or without treatment has been swollen by extravasated blood or by unreleasable intracellular water to a certain end point, the patient dies.

From this material we cannot draw any direct conclusions as to the relative efficacy of various therapeutic procedures. Some conclusions as to pathogenesis, however, may be drawn, and by these conclusions certain lines of therapeutic effort are at least suggested. The patient with an injured head is suffering primarily from uncontrolled internal hemorrhage within the cranial cavity. As the multiple extravasations of blood, together with some intracellular binding of water and the ventricular dilatation, begin to swell the brain, there is a spontaneous effort on the part of the brain tissue, even without treatment, to compensate by decreasing the fluid in the subarachnoid spaces and by decreasing the quantity of intercellular fluid within the brain substance. Lumbar puncture could assist in the first process and intravenous sucrose in the second. When the damage has been too great, both the spontaneous and applied therapeutic mechanisms fail, and the patient dies.

Dehydration is the proper treatment, but perhaps some agent is needed which will more effectively than sucrose split intracellular fluid from within the brain cells. Yet one must recognize that the water binding may be in part a salutary, physiologic defense reaction of the injured cells and that it should not be disturbed too vigorously. It may be that the limits of usefulness of chemical methods of dehydration have been reached.

The dilatation of the lateral ventricles by the brain swelling shutting off the foramens is significant. Relief of the internal traumatic hydrocephalus by ventricular puncture and drainage may be a useful approach in correcting cerebral compression.

Procedures to decrease parenchymatous hemorrhage are of unquestioned value. These include: (1) absolute rest; (2) avoidance of abrupt reduction of intracranial pressure by lumbar puncture within the first six hours, because it is just this pressure which diminishes hemorrhage; (3) limitation of intravenoclysis at first to small quantities, 300 to 400 cc., because raising the blood pressure might cause recurrence of hemorrhage; and (4) for patients in extreme shock, small blood transfusions.

CONCLUSIONS

1. In autopsic material, the subarachnoid fluid in cases of trauma to the head is not increased but decreased.

2. The ventricular fluid is increased in the presence of internal traumatic hydrocephalus.

3. The brain in an injured head at death is not wet but dry; it is swollen but not edematous.

4. Part of the enlargement of the brain in cases of head trauma is a result of ventricular distention.

5. Part of the swelling of the brain after trauma to the head is accounted for by increased blood content from innumerable petechial hemorrhages. (This increment was computed from determinations of iron in the brain specimens. The method did not separate intravascular from extravascular blood. The findings are relative, because the non-hematic iron fraction was not separated from the hematic iron. Further analysis by the experimental method is outlined.)

6. For the remainder of the swelling of the brain in cases of trauma to the head the factor of unreleasable intracellular parenchymatous fluid can be assumed only by exclusion.

7. The lines of therapeutic effort suggested by this study indicate that lumbar puncture and dehydration are indicated but have probably been carried as far as possible. Ventricular drainage may be useful. Emphasis is placed on measures to reduce parenchymatous hemorrhage within the brain substance.

EXPERIMENTAL PRODUCTION OF TUMORS OF THE BRAIN WITH THE SHOPE RABBIT PAPILLOMA

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Cutaneous papillomas developing in rabbits inoculated with the virus of infectious papillomatosis [1] possess the characters of mammalian tumors [2] and are readily susceptible to autotransplantation. Bits of washed papilloma tissue implanted in muscle, subcutaneous tissue and inner organs of the host proliferate actively, invading or displacing adjacent tissue. In the absence of bacterial infection, cellular reaction about the growing implants is notably scanty; frequently none is present. Under these conditions the growth is a slowly enlarging mass which has little apparent effect on the surrounding tissues other than that attributable to pressure or to physical interference. This character of the transplanted papilloma has suggested its use in the study of the effects of pressure inside the cranial cavity. With this in mind, the behavior of the papilloma on implantation in various sites within the skulls of domestic rabbits has been studied. The results obtained are described in the present paper.

From the Department of Surgery and the Laboratory of Experimental Neurology, the Duke School of Medicine.

1. Shope, R. E., and Hurst, E. W.: Infectious Papillomatosis of Rabbits, with a Note on Histopathology, J. Exper. Med. **58**:607-624 (Nov.) 1933. Beard, J. W., and Wyckoff, R. W. G.: The Isolation of a Homogeneous Heavy Protein from Virus-Induced Rabbit Papillomas, Science **85**:201-202 (Feb. 19) 1937.

2. Rous, P., and Beard, J. W.: A Virus-Induced Mammalian Growth with the Characters of a Tumor (the Shope Rabbitt Papilloma): I. The Growth on Implantation Within Favorable Hosts, J. Exper. Med. **60**:701-722 (Dec.) 1934. Beard, J. W., and Rous, P.: II. Experimental Alterations of the Growth of the Skin; Morphological Considerations; the Phenomena of Retrogression, ibid. **60**: 723-740 (Dec.) 1934. Rous, P., and Beard, J. W.: III. Further Characters of the Growth; General Discussion, ibid. **60**:741-766 (Dec.) 1934; The Progression to Carcinoma of Virus-Induced Rabbit Papillomas (Shope), ibid. **62**:523-548 (Oct.) 1935.

METHOD

The virus employed in the production of papillomas for transplantation was obtained from warts occurring spontaneously in cottontail rabbits. Warts which had been stored in 50 per cent glycerin solution for several months were rinsed in distilled water, ground in the usual way with sand and extracted in a 5 per cent suspension with 0.9 per cent sodium chloride solution. Cleared of gross particles by low speed centrifugation, the suspension was filtered by suction through a Berkefeld N candle. An abdominal area about 3 cm. in diameter was shaved, lightly scarified with sandpaper and inoculated by rubbing into it a few drops of the virus suspension.

The histologic structure of the cutaneous papilloma has been described in detail.[3] In brief, the virus causes rapid proliferation of the epidermal cells of the innermost or basal layer, giving rise to protruding papillae. With broadcast inoculation of the virus, as in the present instance, the papillae coalesce, and the growth appears eight to twelve days after inoculation as a confluent layer of papilloma tissue.

When the layer had reached a height of 1 or 2 mm. the fine hair in and about the growth was removed with dilute barium sulfide. The area was gently scrubbed with soap, thoroughly rinsed in running tap water, dried with sterile sponges and then wet with 70 per cent alcohol. With a razor which had been kept in 70 per cent alcohol for thirty minutes the superficial layer of the growth was sliced off; this was discarded. The deeper layer was then shaved away in a thin slice, placed in 1 cc. of sterile 0.9 per cent sodium chloride solution and thoroughly hashed with knives.

Through a midline incision in the scalp, an opening 1.5 mm. in diameter was made in the skull in the desired region. Implantation directly into the brain was accomplished by injection of a few of the fragments of papilloma through a short 18 gage needle ground smooth at the end. When extradural implantation was intended, the dura was gently separated intact from the skull, and a few fragments of papilloma tissue were pushed with a probe through the opening in the skull. For subdural implantation the dura was punctured without separation from the skull, and fragments were pushed gently through the opening with a probe. In the last instance, dural incision was confirmed by the appearance of subarachnoid fluid. The defect in the bone was closed with wax containing a fragment of lead for roentgenographic localization, and the incision in the scalp was closed with silk. Strict precautions for the maintenance of asepsis were observed throughout.

The rabbits were allowed to live for varying periods subsequent to transplantation; they were killed by means of illuminating gas.

GENERAL CHARACTER OF GROWTHS RESULTING FROM INTRACRANIAL TRANSPLANTATION

The papilloma proved readily transplantable to the subdural space. Growths produced in this region in rabbits DR 97 and DR 598, killed forty-one and forty-two days respectively after subdural implantation, are shown in figures 1 and 2. The growths in both instances were

3. Footnotes 1 and 2.

situated directly beneath the original osseous defects, and their location in relation to the cortex corresponded to the rostral portion of Brodmann's area 17 as demarcated for the rabbit brain.[4] The masses were firmly embedded in the cortex, could not be dislodged by gentle manipulation and were covered by dura except in the region of the original incision, where the membrane appeared adherent to them. In shape they were flattened spheres; they were elastic and well encapsulated, and the presenting surface of each was irregular and creamy white. On section the external layer and its inward extensions showed as a

Fig. 1.—Subdural tumor, × 2.

rind of whitish living tissue about a dense, concentrically striated creamy or grayish black necrotic mass. No connective tissue capsule was evident on macroscopic examination. Although the masses were adherent to the underlying cerebral tissue, transition from developing nodule to cortex was very abrupt. The papillomatous pattern was recorded externally by blunt irregularities of the proliferating basal epithelium.

4. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues, Leipzig, Johann Ambrosius Barth, 1909, vol. 12, figs. 106 and 107.

This was represented in the interior by sharper papillae that penetrated the necrotic center. The proliferative activity of the external layer appeared unimpaired, but there was a distinct inability on the part of the epithelial columns to invade the surrounding tissue. There was no change in the portion of the skull adjacent to the tumors.

The subdural tumor from rabbit DR 97 measured 7.2 by 6 by 10 mm. Its outer surface protruded 3 mm. above the surrounding cortical tissue, and its inner surface impinged on the ventricular wall, causing a decided

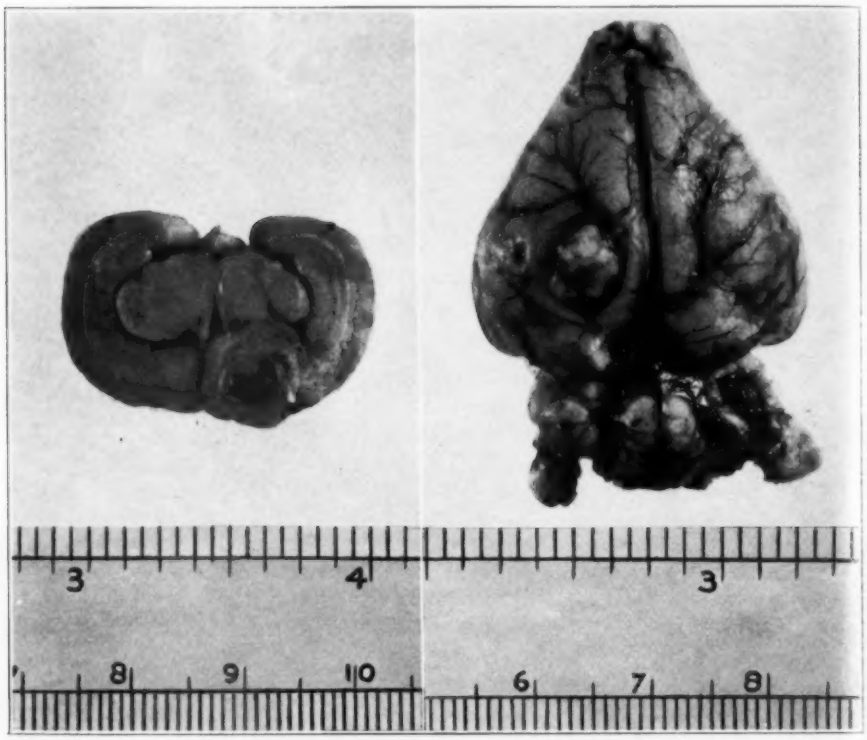

Fig. 2.—Subdural tumor, × 2.

distortion of the ventricular system. The tumor nodule produced in rabbit DR 598 measured 6 mm. in diameter and 4 mm. in cross section. It protruded 2 mm. above the surrounding cortical tissue and involved only the gray matter of the cortex in its growth. The proliferating epithelial layer in the smaller tumor was more regular than that in the larger nodule. The disparity in size or rate of growth of the masses in the 2 animals during the same period may be attributed to the development of the tumor from a single focus in the latter rabbit rather than from the coalescence of multiple foci, which probably occurred in the former.

Extradural implantation of the papilloma likewise resulted in the production of typical, actively proliferating transplants in 2 animals, rabbits DR 98 and DR 99, killed forty-two days and twenty-one days, respectively, after extradural implantation. One such growth is shown in figure 3. The growths, situated over the rostral part of area 17 of the cortex, in both instances were attached to the skull and were covered by a continuous dural sheet adherent to their surfaces. The dural surface of each mass was smooth, exhibiting only faint irregularities suggestive of the papillomatous character of the growth. No gross

Fig. 3.—Extradural tumor, × 2.

reaction was evident in the dura. The growths were not attached to the cortex, and when they were removed a smooth, oval indentation was left in the brain tissue. On section, these extradural nodules were similar to those produced by subdural implantation.

The extradural implantation in rabbit DR 98 was made over the left hemisphere by pushing the hashed papilloma tissue into place with a probe. When the brain case was removed, a column of proliferating epithelium was observed to have penetrated the osseous defect externally and to have produced a small growth, measuring 4 mm. in diameter,

outside the skull. The extradural mass was 7.5 by 8.5 by 6 mm., and the indentation in the cortex was 4 mm. in depth. In rabbit DR 99, implantation outside the dura was made on the right side; on the left

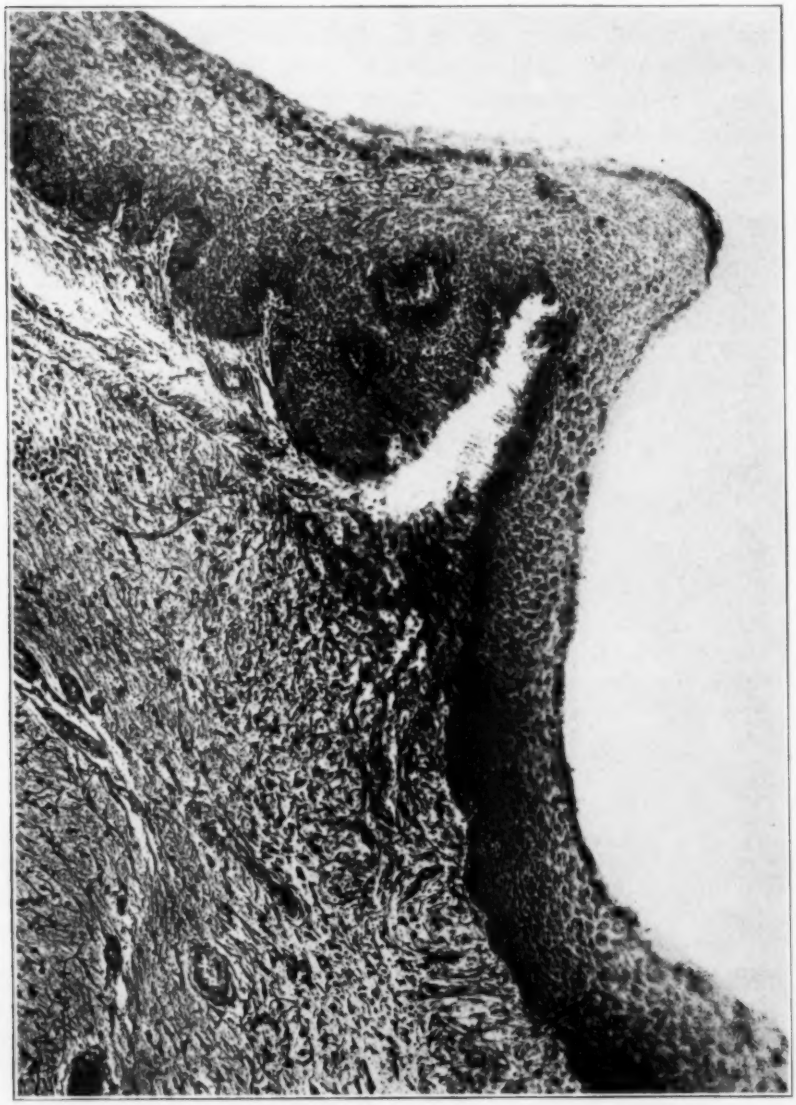

Fig. 4.—Astrocytic reaction to subdural tumor in rabbit DR 98. Silver-lithium carbonate stain; × 230.

side, however, fragments of papilloma were injected directly into the brain tissue through an 18 gage needle. No tumor developed on this side. The extradural growth over the right cerebral cortex was approxi-

mately 4 mm. in diameter. It was dislodged during the removal of the bone case, and more accurate measurements were not obtained. The indentation in the cortex was correspondingly shallow, being scarcely 2 mm. in depth.

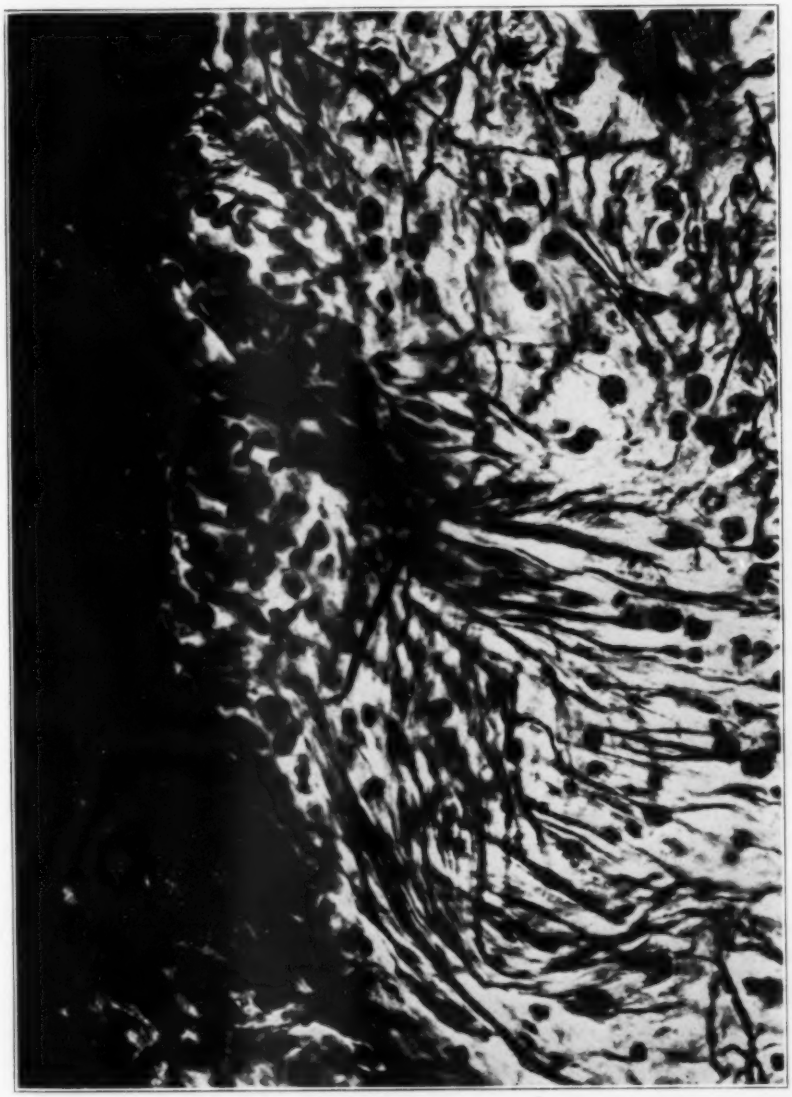

Fig. 5.—Astrocytic reaction to subdural tumor in rabbit DR 98. Silver–lithium carbonate stain; × 485.

Attempts were made to implant the papilloma intracerebrally in 2 other rabbits (DR 415 and DR 402) by injecting fragments of papilloma directly into the brain tissue through an 18 gage needle. Sixteen days

and eighteen days after implantation, respectively, the animals were killed. No intracerebral tumors were found. In rabbit DR 415 a tiny extradural nodule was found at the site of injection.

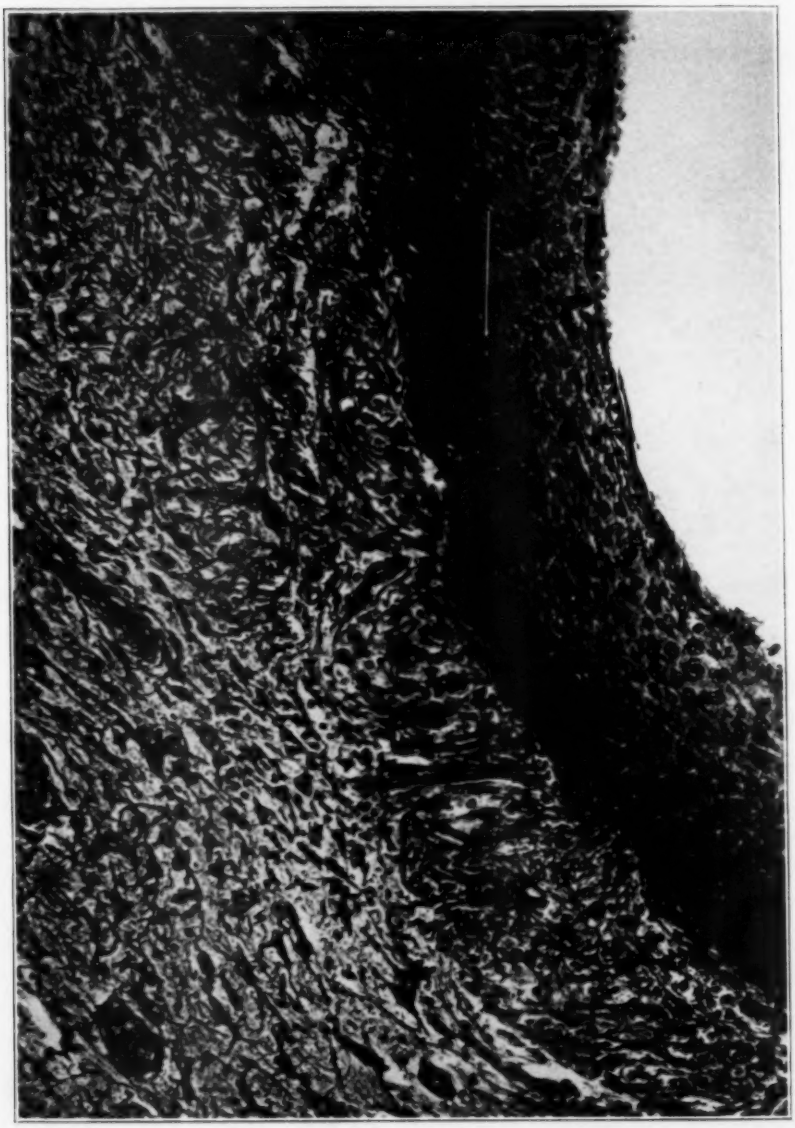

Fig. 6.—Astrocytic reaction to subdural tumor in rabbit DR 98. Silver–lithium carbonate stain; × 375.

REACTION OF CEREBRAL TISSUE TO THE IMPLANTED PAPILLOMA

Specimens were cut through the center of the transplants or through the cerebral defects caused by the extradural masses, and the tissues

were fixed in Cajal's formaldehyde–ammonium bromide solution. Blocks were taken and frozen sections cut to include growths and adjacent brain tissue. These were stained, after the appropriate time of fixation, with

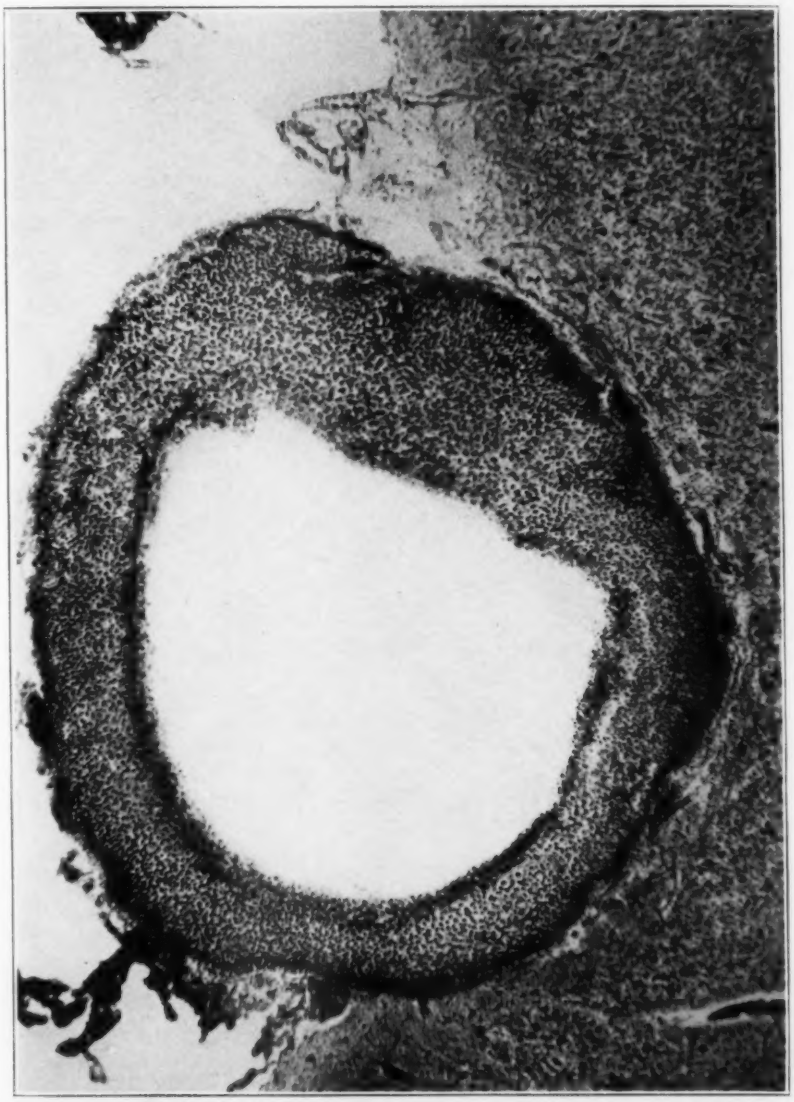

Fig. 7.—Subdural tumor of rabbit DR 598, showing early glial reaction. Silver–sodium carbonate stain; × 145.

(1) Penfield's second modification of Rio-Hortega's silver sodium carbonate stain[5]; (2) Rio-Hortega's silver–lithium carbonate stain, and

5. Penfield, W.: A Method of Staining Oligodendroglia and Microglia (Combined Method), Am. J. Path. **4**:153-157 (March) 1928.

(3) Cajal's gold chloride sublimate method. Other blocks were taken for staining with hematoxylin and eosin.

A part of the subdural growth of rabbit DR 97 was separated from the brain by a thin membrane of pia mater. In some areas this was

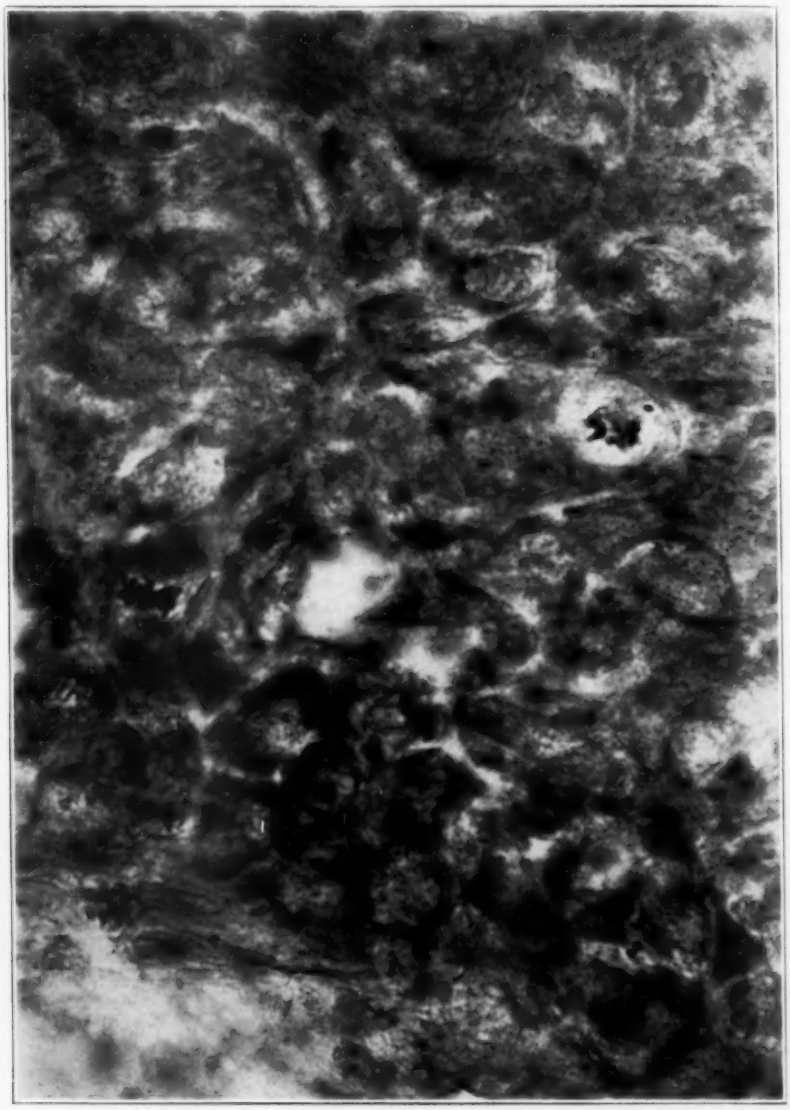

Fig. 8.—Mitotic figures in transplanted tumor of rabbit DR 598. Silver–sodium carbonate stain; × 485.

absent, and the tumor cells were in direct contact with the depressed cortex. The glial reaction was very different in these two regions. Where the pia was present there was no noticeable change in either the

microglia or the astrocytes beneath it; even the microglia lying adjacent to the pial membrane appeared normal. In areas where there was no membrane between the tumor and the brain, marked and extensive glial reaction was present. There was proliferation of fibrous astrocytes with

Fig. 9.—Compression of brain by extradural tumor of rabbit DR 98. Silver–sodium carbonate stain; × 65.

formation of a dense mass of glial fibers (figs. 4, 5 and 6). These fibers were attached to the tumor, and many individual fibers could be seen surrounding one or more of the tumor cells. Only in rare instances did the fibers penetrate into the tumor. This sharp demarcation between

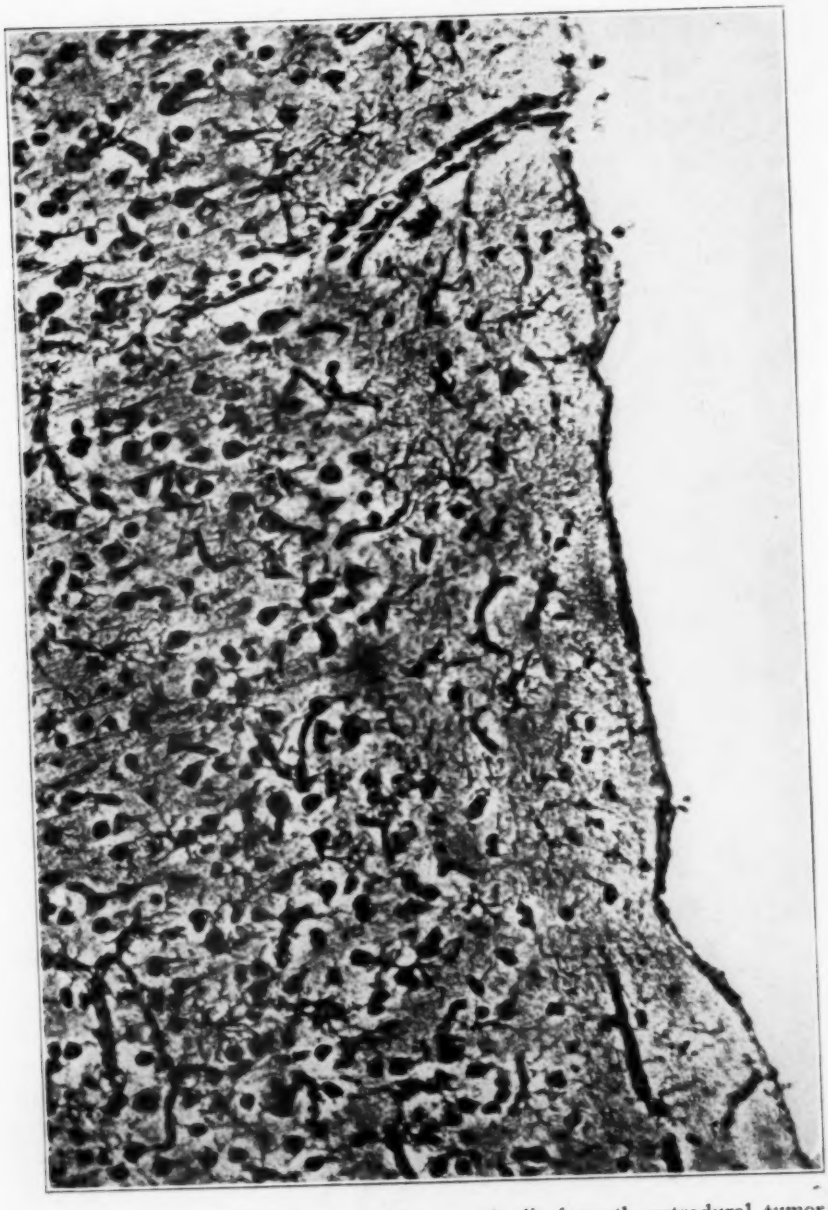

Fig. 10.—Increased cellularity with normal glia beneath extradural tumor in rabbit DR 98. Silver–sodium carbonate stain: × 230.

the astrocytic fibers and the tumor was clearly demonstrated in the specimens stained with gold chloride sublimate; in these the processes were stained deeply, and the tumor was very pale. The cortical neurons were obviously destroyed in the areas of dense gliosis. Many astrocytes with abnormally large cell bodies were lying next to the tumor.

There was uniformly a striking increase in the number of small blood vessels in the outer margin (away from the tumor) of this gliosis. A number of these vessels showed intimal and adventitial thickening suggestive of that commonly seen in association with glioblastoma multiforme in man. In one area there was thrombosis of several medium-sized vessels. Here the astrocytes were larger and their processes were fragmented (clasmatodendrosis). Also, in this area the microglia showed all changes, from thickening of the processes of the cells near the edge of the area to typical compound granular corpuscles (*Gitterzellen*) in the center. This region presented the usual picture of cerebral necrosis. Elsewhere the microglia appeared unchanged.

The tumor of rabbit DR 598 was much smaller than that of rabbit DR 97. Changes similar to those described for the latter were present, but to a lesser extent. The dense glial reaction was just beginning to form (fig. 7). In both tumors many mitotic figures were present in the tumor cells (fig. 8). The papillomas remained discrete, however, and the neoplastic cells did not invade the brain.

The extradural tumor of rabbit DR 98 had greatly compressed the adjacent gray matter, as may be seen in figure 9. The compressed area stained less deeply with the silver sodium carbonate stain. No cellular changes were seen in the neuroglia or microglia. The photomicrograph (fig. 10) was taken at the square marked on figure 9 and shows normal microglia lying next to the tumor. There was, however, increased cellularity in the cortex beneath the tumor, apparently caused by compression only. The cell bodies of the cortical neurons were apparently unchanged by the compression; however, we cannot be certain of this with the stains used for this tissue. The apical dendrites of the neurons were shortened, often curved and occasionally tortuous ("corkscrew processes"). No increased vascularity was seen; the fact that the microglia cells were normal would indicate that the flow of blood through this area had been diminished little if at all for any appreciable length of time.

SUMMARY

Experimental intracranial tumors have been produced in rabbits by extradural and subdural implantation of the cutaneous papilloma induced by the virus of infectious papillomatosis. The intracranial growths were similar in gross characteristics to those observed following transplantation of the papilloma in other organs and in other tissues of the rabbit.

In contrast to the behavior of the growth on implantation in other tissues, with the possible exception of the kidney and the stomach,[2] there was noted an inability of the proliferating epithelium to invade adjacent tissue. When even a thin layer of meninges lay between the tumors and the brain, there was a minimum of glial reaction present. On the other hand, whenever the tumor came in direct contact with the brain, there was astrocytic proliferation with the formation of numerous fibers, many of which were attached to the tumor. Where such gliosis was heaviest there was increased vascularity, and thrombosis occasionally occurred, producing localized areas of necrosis with microglial reaction.

The growth characters of this transplanted cerebral tumor suggest its use in the study of various problems involving intracranial pressure as they may be applied to the central nervous system of the rabbit. Indeed, the tumor appears to offer suitable material for the study of tissue response to slowly developing pressure in any region in which successful implantation can be accomplished. Immediate problems related to the central nervous system are the production of papillomatous tumors within the substance of the brain and a further and more detailed study of the reaction of the brain to the transplants and to prolonged pressure.

THE SUPERIOR COLLICULI

THEIR FUNCTION AS ESTIMATED FROM A CASE OF TUMOR

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AND
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The function of the collicular bodies of the quadrigeminal plate in man, and particularly that of the superior (or anterior) colliculi, remains undetermined. Not only has little experimental work been devoted to the problem, but little suitable human material has been available for study. The case which will be reported here seems ideal in many respects, and we feel that its presentation is worth while.

COMPARATIVE ANATOMY AND PHYSIOLOGY OF THE COLLICULI

Studies in evolution show that the function and importance of the tectum mesencephali have been steadily regressive.[1] In the very early vertebrates, such as the bony fishes, the tectum consists of a relatively large bilobular body situated on the alar plates that cover the aqueduct. These corpora bigemina (in selaceans) are exclusively visual in function. The expanded portion of the alar plates serves as the end station of the somesthetic pathway.

Beginning with the amphibians and progressing through reptiles and birds, two more colliculi make their appearance, i. e., the inferior colliculi, which subserve a function of audition. Even in birds, however, the superior colliculi are the association centers of vision and assume such importance in this respect as to be termed the lobus opticus.

The importance of the tectum mesencephali in these vertebrates can be understood when one realizes that it is the associational mechanism for visual, auditory and somesthetic reflexes. It is not surprising to find that its cellular structure is complex. Cajal resolved the lobus opticus in birds into three series of strata: an external formation of seven layers of nerve cells and fibers, an intermediate formation of five layers and an internal formation of two layers. The first stratum is a layer of optic fibers derived from the optic tract.

From the Department of Surgery, Neurosurgical Service, College of Medicine, State University of Iowa.

1. Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, ed. 2, New York, Paul B. Hoeber, 1923, pp. 485-525 and 782.

As the mammal is approached, however, this great complexity and importance are lost to such an extent that the corpora quadrigemina appear almost vestigial. Thalamization (which begins in birds) and telencephalization rob the tectum of its visual, auditory and somesthetic importance.

One can hardly doubt, however, that these bodies continue to function in man in certain reflex capacities.

AFFERENT AND EFFERENT CONNECTIONS OF THE COLLICULI

The superior colliculi present an outer stratum zonale and three gray strata. The cortex is the homologue of the cortex of the optic lobe in birds.

Afferent Connections of the Superior Colliculi (fig. 1).—1. Fibers running from the retina through the optic tract (these constitute a small

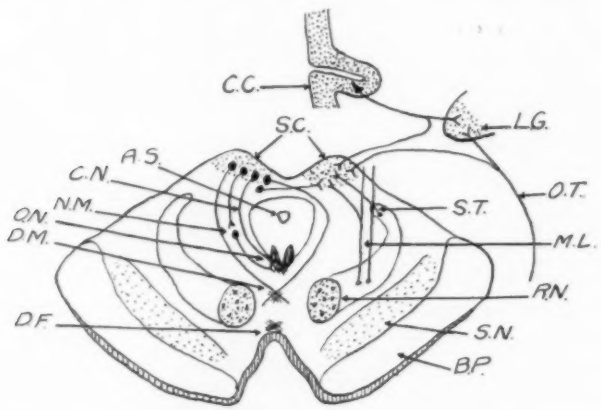

Fig. 1.—Diagrammatic representation of the better known connections to and from the superior colliculi. Afferent connections are shown on the right and efferent connections on the left. *C.C.*, calcarine cortex; *S.C.*, superior colliculi; *L.G.*, lateral geniculate body; *O.T.*, optic tract; *S.T.*, spinotectal tract; *M.L.*, medial lemniscus; *R.N.*, red nucleus; *S.N.*, substantia nigra; *B.P.*, basis pedunculi; *D.F.*, decussation of Forel; *D.M.*, dorsal tegmental decussation of Meynert (fountain decussation of Meynert). This tract proceeds as the praedorsal bundle and tectospinal tract. *O.N.*, oculomotor nuclei; *N.M.*, nucleus of the medial longitudinal fasiculus; *C.N.*, colliculonuclear tract to the nuclei of the extraocular muscles; *A.S.*, aqueduct of Sylvius.

proportion of optic fibers, and none of them subserve the function of vision).

2. Fibers from cells about the calcarine fissure.

3. Fibers from the spinotectal tract.

4. Collaterals from the medial lemniscus (probably proprioceptives from muscles and tendons).

Efferent Connections of the Superior Colliculi.—1. Fibers from the superior colliculus to the nuclei of the oculomotor mechanism (the colliculonuclear tract). Arising from large cells in the fourth layer, one portion decussates (fountain decussation of Meynert) and one portion continues direct. The fibers end in the nuclei of the oculomotor, trochlear and abducens nerves.

2. The tectospinal tract, which passes by way of the internal arciform fibers to the dorsal tegmental decussation of Meynert. It descends, in relation with the posterior longitudinal fasciculus, into the ventral white column of the spinal cord.

The following paragraph is taken from Rasmussen:[2]

> The better known connections of the superior colliculus (primary visual reflex center) consist of fibers from the optic tract, from the visual cortex and from the spinal cord (spino-tectal fasciculus). Collaterals from other tracts passing up and down also enter the superior colliculus. From the nucleus of the superior colliculus fibers go to the various centers, including the nucleus of the posterior commissure and the nucleus of the medial longitudinal fasciculus, (centers connected with ocular movements, with the vestibular system and with the corpus striatum), the oculomotor and trochlear nuclei, the pons (by means of fasciculus tectoponticus), and the spinal cord (by means of fasciculus tectospinalis). The nucleus of the medial longitudinal fasciculus, in turn, discharges downward into lower centers. The center for upward gaze and associated movement of the eyelids and raising of the brow is generally considered to be in the neighborhood of the superior colliculus, most likely in the dorsal part of the reticular formation just lateral to the upper end of the oculomotor nucleus.

Afferent Connections of the Inferior Colliculi.—Fibers from the lateral lemniscus of the homolateral and of the contralateral side.

Efferent Connections of the Inferior Colliculi.—Fibers running by way of the inferior brachium to the tegmentum of the cerebral peduncle and thence to the thalamus and cortex of the temporal lobe.

Both pairs of colliculi have commissural connections.

FUNCTION OF THE SUPERIOR COLLICULI

The superior colliculi have been thought to play a role in two important functions: (1) the pupillary light reflex and (2) the associated or conjugate movements of the eyes. Controversy has arisen concerning each of these functions.

For purposes of analysis and comparison, we have given some attention to observations recorded in cases of tumor of the pineal gland and of tumor of the third ventricle.

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2. Rasmussen, A. T.: The Principal Nervous Pathways, New York, The Macmillan Company, 1932.

REVIEW OF REPORTED CASES OF TUMOR OF THE QUADRIGEMINAL PLATE

Most of the tumors of the quadrigeminal plate which have been reported were discarded because they were obviously too extensive to be of analytic value. In table 1 a list of cases is given in which the lesion appears to have been reasonably limited to the tectum. There was practically no impairment of the pupillary light reflex. What mention was made of associated movements implied that they were impaired or lost.

Wilson and Gerstle [3] reported 2 cases which might serve for more detailed elaboration. These authors were more interested, however, in defending the claim that tumor can cause Argyll Robertson pupil.

TABLE 1.—*Tumor of the Quadrigeminal Plate*

	Pupillary Reaction		Associated Movements	Tumor	Comment	Author
	Light Reflex	Accommodation				
1.	Good	?	Poor	Confined to Q. plate posterior to aqueduct	.....	Bristowe [8]
2.	Good	?	?	Tubercle of Q. plate extending to pons	3d nerves paretic	Kolisch [8]
3.	Good	Good	Bilateral ophthalmoplegia	Tubercle of Q. plate	.....	Sachs [8]
4.	Good	Good	?	Tubercle, size of hazelnut posterior to aqueduct	.....	Goldzieher [8]
5.	Good	?	?	Gliosarcoma of Q. plate	Pupils unequal; patient partly blind	Taylor [8]
6.	Very sluggish	Very sluggish	?	Large glioma of Q. plate	Pupils irregular and dilated; nystagmus	Glaser *
7.	Good	Good	?	Walnut-sized glioma of Q. plate	Internal strabismus	Glaser *

* Glaser, M. A.: Brain **52**: 226-262, 1929.

Their first patient exhibited widely dilated pupils which did not react to light directly or consensually. Reaction to accommodation was prompt. Ocular movements were limited and poorly sustained both to right and to left, although upward and downward associated movements appeared normal. There was slight internal strabismus of the right eye, with ptosis of the right lid and nystagmus on deviation to the right. At postmortem examination, however, it was seen that the tumor, in addition to having destroyed the anterior colliculi, filled the fourth ventricle and invaded the pons.

3. Wilson, S. A. K., and Gerstle, M.: Argyll Robertson Signs in Mesencephalic Tumors, Arch. Neurol. & Psychiat. **22**:9-18 (July) 1921.

Their second patient also showed absence of the pupillary light reflex without impairment of the accommodation reflex. Conjugate upward deviation of the eyes showed pronounced limitation. Conjugate lateral movements were of good range except for some defect in lateral movement of the left eye. Associated downward movements were fair. At autopsy, however, there was revealed a large cystic tumor which, in addition to flattening the left anterior colliculus, extended into the anterior portion of the thalamus and reached from the upper limit of the pons to the corpus callosum.

In a like manner, Wilson and Rudolf [4] reported a case of Argyll Robertson pupil. Conjugate lateral movement of the eyes was well performed to the right but poorly performed to the left. Upward associated movement was poor and downward associated movement impossible. Autopsy revealed a tumor invading the splenium of the corpus callosum and starting to grow into the third ventricle. The ventricular aspect of both thalami and the hypothalamus were invaded. The authors stated that, most significant of all, the tumor had invaded and destroyed the anterior colliculi and that the signs pointed unmistakably to invasion of this region.

Tumor of the Pineal Body.—Among the signs attributed to this tumor are ptosis, loss of upward associated movements of the eyes and macrogenitosomia praecox in young boys. The first two of these signs have been thought to be due to pressure on the superior colliculi.

A study of these cases (tables 2 and 3) shows that Argyll Robertson pupils are occasionally but by no means commonly found. Ptosis is rare. Impairment of some form of associated ocular movements is not uncommon and is most commonly paralysis of upward associated movements.

Tumor of the Third Ventricle.—In reference to the third ventricle, the following is quoted from a complete paper by Fulton and Bailey.[5]

> Pupillary disturbances are frequently seen. Argyll Robertson pupils have been reported (Ford, 1924) but are more commonly associated with pineal and midbrain tumors. In cases of tumor of the third ventricle, they are probably due to involvement of the mid-brain.
>
> Paralysis of conjugate eye movements was noted by Weisenburg (1911) but are more characteristic of tumors of the mid-brain and pineal body (Horrax, 1927).

Pupillary Light Reflex.—That the Argyll Robertson pupil can be caused by pathologic conditions other than syphilis is well established,

4. Wilson, S. A. K., and Rudolf, G.: Case of Mesencephalic Tumor with Double Argyll Robertson Pupil, J. Neurol. & Psychopath. **3**:140-143, 1922.

5. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:261-277, 1927.

but syphilis (of the tabetic or dementia paralytica type) is by far the commonest cause.

Merritt and Moore [6] reviewed the works of Karplus and Kreidl, Lenz, Ranson and Beattie and concluded that the fibers which subserve

TABLE 2.—*Tumor of the Pineal Gland*

	Pupillary Reaction					
	Light Reflex	Accommodation	Associated Movements	Tumor	Comment	Author
1.	Good	?	Poor	Tumor 3.5 × 2 × 1.5 cm.	Bilateral paralysis of 6th nerve	Glaser *
2.	Good	?	?	Tumor 2.5 cm. in diameter	Embedded in the Q. plate	Dandy †
3.	Good	Good	Unable to elevate eyes	Parapineal tumor 2.8 cm. in diameter	Paralysis of the right 6th nerve	McLean ‡
4.	Poor	Good	?	Tumor size of walnut	.....	Harris §
5.	Absent	Good	Good	Tumor 2.5 cm. in diameter	Bilateral paralysis of external rectus	Globus and Silbert #
6.	Sluggish	?	Limitation of upward gaze	Tumor 2 × 2 × 3 cm.	Paralysis of right external rectus	Globus and Silbert #
7.	Absent	Good	Paralysis of upward gaze	Large tumor	Ptosis of right eyelid; weakness of right external rectus	Globus and Silbert #
8.	Sluggish	?	?	Tumor 7 × 6 × 8 cm.	Ptosis of right lid; paresis of external recti	Globus and Silbert #
9.	Sluggish	Good	?	Tumor, 5 cm. in diameter	Bilateral weakness of internal rectus	Globus and Silbert #
10.	Sluggish	?	Lost to right	Large cystic tumor	Ptosis of right lid; patient became deaf	Globus and Silbert #

* Glaser, M. A.: Brain **52**: 226-262, 1929.
† Dandy, W. E.: Arch. Surg. **33**: 19-46, 1926.
‡ McLean, A. J.: Surg., Gynec. & Obst. **61**: 523-533, 1935.
§ Harris, W., and Cairns, H.: Lancet **1**: 3-8, 1932.
# Globus, J. H., and Silbert, S.: Arch. Neurol. & Psychiat. **25**: 937-985, 1931.

TABLE 3.—*Summary of Ocular Signs Associated with Tumors of the Pineal Gland* *

Blindness or impairment of vision	45	Conjugate deviation	3
Diplopia	16	Paralysis of fourth cranial nerve	3
Paralysis of upward movement	15	Paralysis of all extraocular muscles	3
Paralysis of sixth cranial nerve	15	Paralysis of downward movement	3
Immobility of one or both pupils	14	Unilateral ptosis	3
Nystagmus	12	Bilateral ptosis	3
Internal strabismus	5	External strabismus	1
Paralysis of third cranial nerve	4	Constriction of pupil	1
Argyll Robertson pupils	3	Rhythmic convergence spasm	1

* Taken from a paper by K. O. Haldeman (Tumors of the Pineal Gland, Arch. Neurol. & Psychiat. **18**: 724-744 [Nov.] 1927). The paper is a complete report of 113 cases of tumor of the pineal gland, taken from the literature to 1927.

6. Merritt, H. H., and Moore, M.: The Argyll Robertson Pupil: An Anatomic-Physiologic Explanation of the Phenomenon, with a Survey of Its Occurrence in Neurosyphilis, Arch. Neurol. & Psychiat. **30**:357-373 (Aug.) 1933.

the light reflex pass from the optic tract with the brachium of the superior colliculus to the cephalad end of the superior colliculus. A portion of the fibers cross in the dorsal portion of the posterior commissure while the remainder arch ventrally toward the oculomotor nuclei.

Paralysis of Associated Ocular Movements.—The influence of the cortex on ocular deviation deserves brief consideration here. Conjugate deviation as a result of irritative and destructive lesions of the cortex is demonstrated, to be sure, in epileptic seizures and sudden destructive lesions. The effects are transient because of bilateral representation of voluntary ocular movement. The existence of cortical "eye turning centers" in the frontal, temporal and occipital lobes has been definitely established. Those in the temporal and occipital lobes are probably associated with cortical auditory and visual functions, respectively. The cerebral cortex, however, has to do with the voluntary direction of visual gaze and not with reflex conjugation or associated movement of the paired visual organ. The function of maintaining the eyes in a conjugate relation is clearly relegated to structures in the mesencephalon. The problem of present concern is whether the superior colliculus subserves or is indispensable to this function.

That the maintenance of conjugate focus is not and cannot be controlled by voluntary effort alone would seem to be clearly demonstrated by a simple experiment: If the visual fields are separated by a partition between the eyes, any existing muscular imbalance quickly renders the eyes aphoric. No amount of voluntary effort can correct the hyperphoria or maintain correction of the esophoria or exophoria.

As one studies motor function, a plan always stands out in clear relief. The cerebral cortex is responsible for the voluntary initiation and direction of movements, but when the muscles are contracted, and while they are being contracted, various phenomena of synergy and coordination are controlled by reflex arcs which begin in the muscle that is being contracted. In the instance of associated ocular movements, the afferent arc begins in the retina.

Spiller [7] stated that the evidence is strong that paralysis of associated lateral movements of the eyeballs is indicative of a lesion of the posterior longitudinal bundle. He also stated that it is true that lateral associated movements have been impaired, with paralysis of upward or downward associated movements, in a number of instances as they were in some of his cases, but a lesion in the vicinity of the corpora quadrigemina will better explain this form of paralysis than will a lesion of the cerebral cortex. He continued that because certain of his

7. Spiller, W. G.: The Importance of Clinical Diagnosis of Paralysis of Associated Movements of the Eye-Balls, Especially of Upward and Downward Associated Movements, J. Nerv. & Ment. Dis. **32**:417-497, 1905.

patients who had lesions in the tegmentum, not involving the corpora quadrigemina, exhibited various forms of associated paralysis a coordinating center in the colliculus is improbable. For example, in a case in which there was paresis of upward associated movement the lesion was posterior to the oculomotor nucleus and did not involve the quadrigeminal plate.

Many cases are cited by Posey and Spiller [8] which presented various combinations of paralysis of association, and in all instances parts in the region of the aqueduct of Sylvius were implicated.

The following summary is quoted from Spiller:[7]

> As a result of my studies, I believe that persisting paralysis of associated lateral movement indicates a lesion of the posterior longitudinal bundle; that persisting paralysis of upward or downward movement indicates a lesion in the vicinity of the oculomotor nucleus, and that paralysis of associated ocular movements is not the result of a lesion of extracerebral nerve fibers. Lesions of the cerebral cortex may certainly cause paralysis of lateral associated ocular movements, and possibly of upward and downward associated ocular movements, but cortical paralysis of associated ocular movements is transitory, unless possibly where the center on each side of the brain is destroyed. Paralysis of associated ocular movements may be caused by hysteria. Any case in which associated ocular palsy is persistent, and is of organic nature, is unsuitable for operation unless the operation is merely palliative, as the lesion is probably within the posterior part of the pons or cerebral peduncle, according to the form of the associated palsy, or else causes much pressure upon the dorsal portions of these structures. The paralysis of associated ocular muscles may be produced by inflammatory lesions or lesions of a similar character (alcohol, syphilis) as well as by tumor, and may disappear later in the course of the disease. Syphilitic ependymitis or cellular infiltration must be considered in diagnosing the lesion causing paralysis of associated ocular movements. Most congenital associated palsies are probably nuclear in origin.

Spiller stated that all the pathologic evidence he had been able to obtain in cases of persistent palsy of upward or downward movement is indicative of a lesion near the aqueduct of Sylvius, and that it is extremely doubtful whether a lesion confined to the corpora quadrigemina and causing no pressure on the surrounding parts ever causes paralysis of associated ocular movements. Those who favor such a view have not produced proof of a supranuclear center in this part.

He quoted Topolanski as saying that electrical irritation of the corpora quadrigemina of the rabbit does not produce ocular movements and that these parts can be removed without producing symptoms.

Bernheimer, cited by Spiller, has shown by experiments on monkeys that normal ocular movements do not depend on the integrity of the

8. Posey, W. C., and Spiller, W. G.: The Eye and Nervous System: Their Diagnostic Relations, Philadelphia, J. B. Lippincott Company, 1906.

corpora quadrigemina, thus refuting Prus's statements that a center for ocular movements does exist in this structure.

Spiller has collected cases in which the corpora quadrigemina have been destroyed without disturbance in the movements of the eyeballs (Weinland; Seidel; Ruel; Nissen, cited by Von Kornilow).

As the converse of the aforementioned phenomena, Oppenheim[9] observed pseudobulbar paralysis in which lateral movements of the eyeballs were impaired in voluntary innervation but were preserved when the patient tried to follow an object or to turn in the direction from which a sound came.

Wilson and Pike[10] while studying nystagmus found that injury to the corpora quadrigemina did not affect nystagmus but did bring about disjunctive coordination of ocular movements.

Other Symptoms and Signs Associated with Tumor of the Quadrigeminal Plate.—Ataxia: In a case reported by Taylor[11] the cerebellum was normal, but the corpora quadrigemina were flattened, gray and gelatinous (gliosarcoma). The symptoms were ptosis, staggering gait, drowsiness, ataxia of the upper limbs, nearly complete double opthalmoplegia and lateral nystagmus.

Bielschowsky, quoted by Posey and Spiller,[8] pointed out that in the presence of tumor of the corpora quadrigemina the incoordination associated with occasional temporal pallor of the disks may cause one to confuse the condition with multiple sclerosis.

Bruns, cited by Posey and Spiller, emphasized the difficulty in differentiating between tumor of the corpora quadrigemina and tumor of the cerebellum, as ataxia and ophthalmoplegia may be caused by a tumor in either location.

Bruns held that if the symptoms begin with ataxia the tumor is probably in the cerebellum, but Nothnagel contended that if ataxia begins before ophthalmoplegia the diagnosis of tumor of the corpora quadrigemina is favored.

In 2 cases of tumor observed by Turner,[12] staggering gait with diplopia and headache were the chief symptoms. In 1 case there was retropulsion.

Drowsiness and yawning, nystagmus and impairment of vision: These are not uncommon signs of tumor of the corpora quadrigemina but are not pathognomonic and are undoubtedly due to the hydro-

9. Oppenheim, H.: Zur Symtomatologie der Pseudobulbärparalyse, Neurol. Centralbl. **14**:40-41, 1894.

10. Wilson, J. G., and Pike, F. H.: The Mechanism of Labyrinthine Nystagmus and Its Modifications by Lesions in the Cerebellum and Cerebrum, Arch. Int. Med. **15**:31-39 (Jan.) 1915.

11. Taylor, F.: Disease of the Corpora Quadrigemina, Lancet **2**:1252, 1893.

12. Turner, W. A.: Localization of Intracranial Tumors, Brain **21**:341, 1898.

cephalus and increased intracranial tension that result from obstruction of the aqueduct.

FUNCTION OF THE INFERIOR COLLICULI

Although the interest of this paper is chiefly centered on the superior colliculi, it may be stated that audition is the only function which has been related to the inferior colliculi from both anatomic and clinical standpoints. There is considerable controversy as to whether the inferior colliculi are indispensable to auditory perception. Cases that would give evidence for both the negative and the positive answer to the question have been reviewed by Posey and Spiller.[8]

REPORT OF CASE

C. H., a white girl aged 9, was referred to the University Hospital in March 1936 by Dr. L. W. Chain of Dedham, Iowa.

The chief complaints were inability to walk, periods of unresponsiveness, divergent squint, headaches and vomiting.

The child had been delivered by the aid of instruments but otherwise delivery was uneventful.

At the age of 1 year she began to walk, but her parents said that she was always unusually "wobbly" on her feet. This was especially noticeable when she became old enough to run. She would drag the right lower extremity, with noticeable elevation of the right hip. There was also a tendency to hold the head tilted to the right. Often, on attempting to run, she would stumble for no apparent reason and fall flat with little attempt to catch herself. She was therefore obliged to stand alone at school, being unable to run and play with other children. This motor instability had progressed rapidly during the past few months, and three weeks prior to her admission to the hospital it was necessary to put her to bed because of her complete inability to stand or walk. If seated in a chair, she remained listless and appeared not to be able to use her muscles.

About one year prior to admission she had had a peculiar attack. While going home from school she fell and lay flat. Although she seemed conscious, she would not respond to the other children. After a few moments she arose and proceeded home with no apparent ill effects. She had had about twelve of these attacks. Her mother stated that in some of them she stiffened, with the arms held down and the head back. She had never had a "shaking convulsion." In several of the recent seizures she had stopped speaking in the middle of a sentence, and while she blankly stared ahead, her limbs had fallen limp. If a question was repeated three or four times during the seizure, she would answer.

When the child was 1 year old her mother noticed a developing squint. A futile attempt was made to correct this by glasses.

Although the child slept well, without ever crying out at night, she had complained of headaches for three years, which were relieved by projectile vomiting. She had never complained of dizziness.

She had appeared more drowsy and sleepy during the past six months, and it was necessary to take her out of school the past year, chiefly because of unresponsiveness. She was in the second grade but always found it difficult to learn and particularly to write.

Recently the vision had become poor. Glasses were of no avail.

For the past six months she had occasionally soiled herself as a result of incontinence.

Family History.—The father and mother were both alive and well. Nine siblings were alive and well; none were dead.

Past History.—In addition to the disturbances brought out in the history of the present illness, she had had a "high fever" at the age of 1½ years, at which time she could "hardly breathe." She had begun to walk at one year and to talk at the usual age. She had talked normally in her earlier years.

The past history was otherwise unessential.

Examination.—The child sat perfectly still in a chair with the extremities laxly remaining in any resting position in which one placed them. She was listless, with no apparent interest in her surroundings and with never the slightest play of emotion on her face. If asked a question repeatedly, she might finally give a brief, somewhat explosive answer in a strikingly harsh bass voice. The answer was sometimes unintelligible.

The largest circumference of the head was 58 cm. The eyes showed a divergent squint of 40 degrees. She fixed at times with one eye and at times with the other. Extraocular movements were complete in all four directions but with obviously disjunctive coordination. There was no ptosis, and nystagmus was not elicited. The pupils were equal and regular in outline, reacted well to light individually and consensually and reacted on an attempt to accommodate. There was bilateral choking of the optic disks (2 to 3 diopters), which the ophthalmologist felt was of recent onset and without hemorrhage. Vision was 6/60 in each eye, and the visual fields appeared full to vis-a-vis examination.

Function of the cranial nerves was unimpaired. (Special vestibular tests were not made.) The sensorium seemed normal throughout to tests for pain, light touch, two point discrimination and sense of position, although one of us (O. H.) felt that there was evidence of astereognosis with respect to the right hand.

Although there was evident laxness of the muscles, with hypotonia of all extremities, the strength was good and the grips were 100 per cent.

Reflexes	Right	Left	
Biceps	++	++	
Knee	+++	+++	(pendular)
Achilles tendon	++++	++++	
Abdominal	0	0	
Plantar	Extensor	Extensor	

The Hoffman sign was present on the right and absent on the left. Ankle clonus was sustained on both sides. Alternate movements were badly performed on both sides and with the tongue. She missed badly in the finger to nose test. When she was placed on her feet and asked to walk, there was marked astasia-abasia, with retropulsion and lateropulsion to the right.

General examination of the systems gave essentially negative results. The temperature was normal; the pulse rate, 80, and the blood pressure, 100 systolic and 75 diastolic. The Wassermann reaction was negative.

Although the findings were strongly suggestive of a cerebellar tumor, the history, disjunctive ocular coordination and bass voice suggested the possibility of a more proximal tumor, particularly a tumor of the pineal body or possibly of the third ventricle. Consequently, a ventriculogram was made. Three hundred and eighty cubic centimeters of ventricular fluid was replaced with air, and the ventriculogram revealed symmetric hydrocephalus and a third ventricle dilated to a degree in keeping with the dilatation of the lateral ventricles. The lateral view

did not demonstrate the outline of the third ventricle sufficiently to rule out a pineal tumor, but the findings were accepted as sufficient to warrant a diagnosis of subtentorial tumor.[13]

Judging from the postmortem examination of the brain, the third ventricle should have exhibited its entire contour but with complete obstruction of the

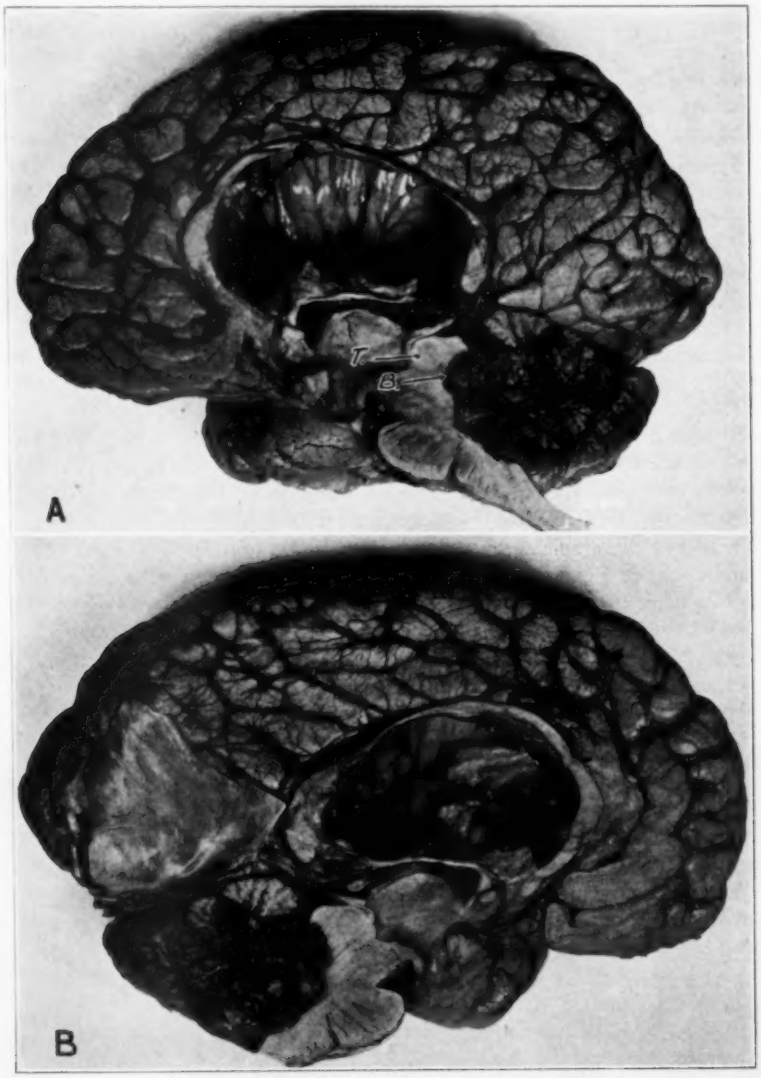
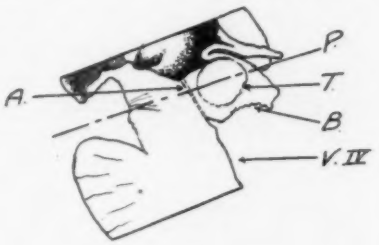


Fig. 2.—The two halves of the brain. *A*, right half; *B*, left half. *T*, tumor, the confines of which are clearly visible; *B*, region of the inferior colliculi from which the biopsy specimen was taken.

13. One of us (O. H.) would no longer accept such an insufficient demarcation of the third ventricle as final but would make further effort to obtain a filling.

aqueduct. This assurance, however, of the absence of a pineal tumor would have had great significance at the time of exploration.

The cerebellum was explored in the usual manner and was found to be devoid of tumor. When air and fluid were released from the ventricles the cerebellum was relaxed, with no tendency to bulge. The vermis was incised in the midline, and a fourth ventricle of normal size was disclosed. An occasional drop of



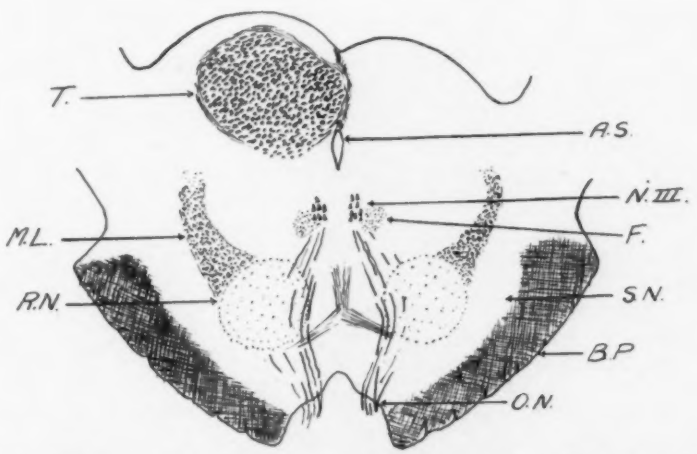


Fig. 3.—Diagrammatic sketches of the mesencephalon. The upper drawing shows only one half of the mesencephalon (mesial view). *A*, aqueduct of Sylvius; *T*, tumor; *B*, region of the inferior colliculi from which a specimen for biopsy was taken; *V, IV*, region of the fourth ventricle; *P*, plane of transverse section from which the diagrammatic sketch below was made. Both halves of the mesencephalon were used in the preparation of the lower sketch, which illustrates the tumor in its greatest diameter and also its relation to the more important structures of the mesencephalon. The cells in the nuclei of the ocular nerves showed no pathologic changes. This was true also of the red nucleus. The fibers in the region of the median longitudinal fasciculus were intact. *T*, tumor; *M.L.*, medial lemniscus; *R.N.*, red nucleus; *A.S.*, aqueduct of Sylvius; *N III*, oculomotor nucleus; *F*, medial longitudinal fasciculus; *S.N.*, substantia nigra; *B.P.*, basis pedunculi; *O.N.*, oculomotor nerve.

cerebrospinal fluid issued from the aqueduct. Realizing that the obstruction was at a high point in the aqueduct, the operator was anxious to determine the possibility of a pineal tumor in view of a subsequent operation through the proper exposure. Had the ventriculogram been sufficient to rule out a pineal tumor, there would have been no anxiety or excuse for proceeding further. When the

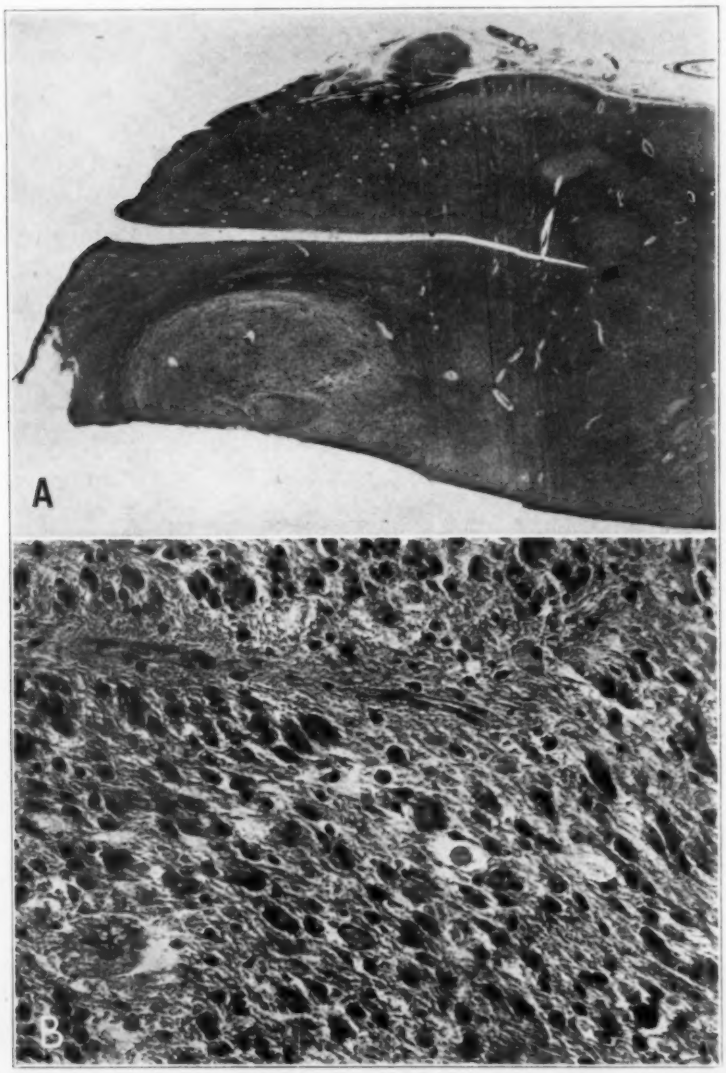


Fig. 4.—*A*, low power photomicrograph of a transverse section of the left half of the mesencephalon (phosphotungstic acid-hematoxylin stain), showing the pseudocapsule and the confines of the tumor. *B*, high power photomicrograph of the section shown in *A*, demonstrating the cellular structure of the tumor.

quadrigeminal plate was reached, a firm globular mass was encountered. Material for biopsy was taken from this in view of the possibility of pinealoma. This later proved to be normal tissue and had been taken from the inferior colliculus.

Shortly after the operation hyperthermia developed, the temperature being 106 F. per rectum, and the extremities were icy cold. There was marked extensor rigidity, with the arms extended and pronated and fists clenched. Cold sponges reduced the hyperthermia, but despite the usual care the patient succumbed fourteen hours after the operation.

Necropsy.—At necropsy a small spherical tumor was observed practically within the confines of the left superior colliculus (fig. 2).

Aside from dilation of the ventricles, nothing unusual was found in the brain. The aqueduct of Sylvius was not completely obstructed. It was patent to a strand of silkworm gut but to nothing larger.

The material for biopsy which had been taken at the time of operation had not included tumor but had been taken from normal inferior colliculus.

Microscopic Studies.—Transverse serial sections were made of both halves of the mesencephalon from just cephalad to just caudad to the tumor. The sections were made 20 microns thick, and every ninth and tenth section was stained with Held's stain and hematoxylin-eosin stain.

Studies of these sections revealed that none of the major nuclei or tracts of the mesencephalon were destroyed except those related to the left superior colliculus (fig. 3).

The pathologic description of the tumor, as given by Dr. Gregory Barer and Dr. William J. Dulin, was as follows (fig. 4): "Situated in the left superior colliculus is a circumscribed oval tumor, measuring between 4 and 5 mm. in its largest diameter. Except for the anterior aspect, the tumor is surrounded by compressed brain tissue, which forms a distinct false capsule. The median posterior raphe is displaced definitely to the right, but the tumor does not invade the right colliculus. Anteriorly the tumor cells can be seen invading normal brain tissue a very short distance.

"The tumor is composed chiefly of large spindle-shaped cells, which tend to have a distinct palisade arrangement. Between these cells is an interlacing mass of fibrils, an occasional large cell suggestive of an astrocyte, and typical tumor giant cells. A rare mitotic figure is present in the spindle-shaped cells. A moderate number of well formed medium-sized blood vessels are observed. No areas of extravasated blood, blood pigment or degeneration are noted.

"The cytologic structure and arrangement resemble more closely the glioblastoma than any other classified type of glioma."

COMMENT

From the foregoing information several facts seem to stand in relief:

1. Although a tumor which extends anterior to the quadrigeminal plate may or may not be associated with a loss of pupillary reflex to light, a tumor which appears to be limited to the superior colliculi or to the quadrigeminal plate is invariably unassociated with this sign.

2. A lesion of the superior colliculi appears to be always accompanied by one or more forms of paralysis of associated ocular movements.

To be sure, lesions variously placed about the aqueduct and anterior to the quadrigeminal plate may cause paralysis of associated move-

ments in various and limited forms. This might be expected and does not dispose of the possibility that the superior colliculus is the "head ganglion" for associated ocular movements.

Our patient had distinct loss of associated movements in all directions, and she fixed with either eye. These disjunctive movements were first noticed at the age of 1 year. In consideration of the remainder of the history, it is reasonable to suppose that the tumor was present at that time and was of such a nature that all signs could be attributed to involvement of the superior colliculus.

The pupillary light reflex was never lost, but from a study of the specimen it could well be that the most cephalad fibers of the colliculus escaped destruction.

While we are reserved about attributing the early ataxia and incoordinate motor phenomena to involvement of the superior colliculi, these signs have been reported in the literature often and consistently enough to deserve some attention, and it is difficult to account for them in this case by any other cause.

In view of the accepted facts concerning the life history of the glioblastoma, it is difficult to correlate the histopathologic character of this tumor with its apparent clinical course.

SUMMARY

A 9 year old girl proved to have a tumor limited to the left superior colliculus of the quadrigeminal plate.

There is clinical evidence that the tumor was present at the age of 1 year.

The pupillary light reflex was present, but there was paralysis of associated ocular movements in all directions. Visual fixation alternated between the eyes.

These, as well as other interesting symptoms and signs, are discussed and correlated with some of the literature concerning the possible function of the superior colliculi.

HEMANGIOMA OF JOINTS

REPORT OF FIVE CASES

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Our purpose is (1) to present 5 cases of hemangioma of the knee joint in which the condition has been diagnosed and treated by us, (2) to set forth the criteria for an accurate diagnosis and the most favorable methods of treatment and (3) to analyze the cases reported in the literature. The peculiar nature of this tumor, the frequency of admitted error in diagnosis and the relative lack of success in its treatment make the 5 cases intensely interesting.

The following series of 5 cases of hemangioma of the knee is the largest reported from any one clinic. To our knowledge radium and roentgen therapy have not been used before in the treatment of this condition. In 2 cases the patients were treated by the accepted methods prior to the use of roentgen therapy. In 3 cases treatment with roentgen rays and radium as suggested by one of us (G. E. B.) gave excellent results.

REPORT OF CASES

CASE 1.—*Extensive synovial hemangioma; attempted excision and eventual amputation.*

E. E., a girl aged 8 years, was admitted to the hospital in December 1915 because of swelling of the left knee, which had been present since the age of 13 months. It was intermittent and at times painful. The family and past histories were irrelevant.

There was bluish mottling of the skin, extending from the left buttock down the side of the leg to the ankle. The left knee was swollen, but there were no other signs.

The knee was explored, and the entire joint cavity found to be filled with a mass of engorged, very thin-walled vessels. An attempt to dissect these free was accompanied by profuse and practically uncontrollable hemorrhage. A tourniquet was applied, and it was necessary to keep the tourniquet on the leg so long that permanent paralysis developed as a result of pressure on the sciatic nerve. Infection developed immediately after the operation.

After a stormy convalescence the infection subsided, but there was a remarkable amount of edema in the leg, with complete motor and sensory loss. No muscle power or sensation was regained below the knee. The child left the hospital with a healthy, granulating and oozing wound and wearing a posterior splint.

Several years later gangrene of the leg developed, for which amputation was necessary.

CASE 2.—*Extensive synovial hemangioma treated with radium.*

M. W., a girl aged 12 years, was admitted to the hospital on July 3, 1929, because of pain and swelling in the knee. She had been first seen at the age of 8 years, when treatment by rest was advised. She returned four years later, still complaining of a painful, swollen left knee. The swelling had not progressed in size but was more painful when the patient was going down stairs. The family and past histories were irrelevant. When the patient was 4 years old her mother noticed an intermittent swelling of the left knee. When this was present there was inability to flex the knee. It had gradually become more painful in the past year, especially during damp weather. There was an occasional sensation of locking in the knee.

Physical examination showed swelling on either side of the patellar tendon, floating patella, thickened synovia, limitation of motion, atrophy of the thigh and calf of the leg and shortening of the right leg to the extent of 0.5 cm. The roentgen findings were negative.

At operation the swelling, just lateral to the patella, was incised, the wall of a bluish gray sac being exposed. A considerable amount of free bleeding was encountered, and reddish, beadlike shiny bits of tissue filled the opening. A free tie was placed around a small mass of tissue and a section removed. The tissue taken for biopsy proved to be that of a hemangioma.

The patient left the hospital in good condition and was given radium treatment. At the time of the present report she has been under observation for eight years. There has been no recurrence.

CASE 3.—*Subsynovial pedunculated hemangioma yielding to easy excision.*

P. M., a boy aged 13, was admitted to the hospital in June 1930 because of pain in the right knee. The family and the past history were irrelevant. Five years previously there had been slight redness and swelling of the right knee, associated occasionally with some pain and stiffness. These symptoms never lasted more than three days. For three years the boy was observed and treated with rest.

The right knee was slightly enlarged over the lateral aspect. There were slight tenderness over the patella, extending to its lateral aspect, and slight restriction of motion, caused by muscle spasm.

At operation a pinkish tissue traversed by dilated tortuous vessels in the subsynovial tissue was exposed. It measured 4 by 2 cm. and was attached to the synovial membrane, merging down to the fibrous tissue at the edge of the external semilunar cartilage. It was removed in toto, with little bleeding.

The wound healed immediately, and the patient was discharged with the leg in a cast.

Up to the present time (six years later) the patient has remained free from symptoms, with no evidence of recurrence.

CASE 4.—*Extensive hemangioma of capsule and synovia treated with roentgen rays.*

M. K., a girl aged 6 years, was admitted to the hospital on Feb. 11, 1935, because of pain and swelling in the left knee, of six years' duration. The family and past histories were noncontributory. At the age of 5 months, when

Fig. 1 (case 4).—Hemangioma of the buttock.

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the patient attempted to stand the left leg was "drawn." There was a slight increase in local heat about the knee, with definite tenderness on palpation and pain on motion. The condition was treated as a "strain" by the family physician, who applied elastic bandages or casts for the recurrent attacks of pain and swelling. These attacks occurred from three to six months apart. During one of them the patient said she felt a "click" in the joint.

A large bluish discoloration was present over the lateral surface of the left buttock and the upper part of the left thigh, which showed an elevated, irregular surface, soft and spongy to palpation (fig. 1). The left knee was swollen. The swelling was localized on either side of the patella and for a distance of 6 cm. above it. This swelling disappeared on elevation of the extremity but recurred

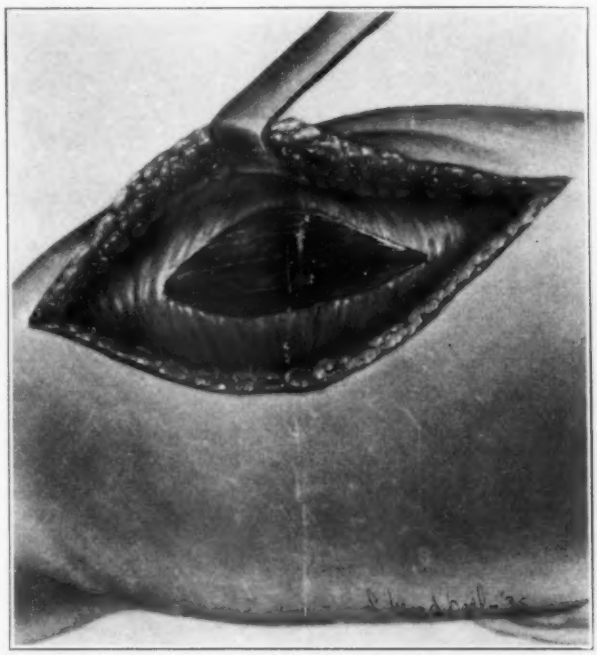

Fig. 2 (case 4).—Wormlike, thin-walled serpentinous vessels involving the capsule of the joint, as seen at operation.

when the leg was put in a dependent position. There was a faint increase in local heat, and the skin on the knee showed a bluish tint. On palpation there was no tenderness, but there was a soft, almost fluctuant sensation. Slight limitation of motion on extreme flexion was noted. Laboratory studies gave negative results. A roentgenogram of the knee showed no abnormality, but a roentgenogram of the thigh showed large, irregular shadows just beneath the skin. Nothing was seen, however, which could be called a phlebolith.

At operation a longitudinal incision was made on the medial side of the patella and carefully carried down through the skin and subcutaneous tissue. Just underlying this, in what seemed to be a capsule, there were wormlike, thin-walled,

knotty, serpentinous bluish vessels (fig. 2). A small tear was made into such a vessel. A number of hemostats were required to control the profuse hemorrhage. By careful dissection it was found that this hemangiomatous tissue extended into the quadriceps muscle. The wound was closed without the taking of a specimen for biopsy. A posterior splint was applied to the leg for two weeks. Healing occurred per primam intentionem.

Roentgen therapy was decided on, and the patient was referred to the Howard A. Kelly Hospital, Baltimore, for treatment. Up to the time of this report she has remained free from symptoms. The knee has returned to practically normal

Fig. 3 (case 4).—Roentgenogram showing erosion of the cartilage and of the tibia and the femur at the capsular attachments.

size, but there are considerable contractures of the hemangiomatous tissue about the joint and slight erosion of the femur and tibia at the insertions of the capsule (fig. 3).

CASE 5.—*Hemangioma treated with roentgen rays.*

J. E. T., a youth aged 18, was admitted to the hospital on Jan. 5, 1937, because of swelling, a sensation of numbness and pain in the right knee on weight bearing, of ninety minutes' duration. The past and the family history were noncontributory.

There was a marked increase of fluid in the joint but no tenderness, relaxation of the joint, inflammatory signs or symptoms or signs of injury. A roentgenogram

disclosed only floating of the patella, indicating increased fluid in the joint. Pure blood was aspirated from the joint. This blood was not clotted or thinned. All laboratory examinations gave negative results.

The joint was explored elsewhere, and a quantity of liquid blood was obtained, which was without clot and more viscous than normal. No mass was found. No postoperative bleeding was encountered.

Subsequent examination showed that the swelling was still present. For this the patient was given high voltage roentgen therapy to a total of 3,200 roentgens. The knee definitely decreased in size until the patient was entirely well and free from symptoms, with normal, painless motion of the joint.

A brief synopsis of our series (table 1) reveals that there were 3 girls and 2 boys. The age at onset varied from eighteen months to eighteen years and the duration of symptoms from ninety minutes to eight years. Trauma was not a factor. Swelling was present in all cases, with pain and recurring attacks of limp and pain on motion in 4. The palpable elastic, spongy mass, compressible and distensible, was evident in only 2. There was tenderness in 2. Muscular atrophy and crepitation were present in only 1 case. Two of the patients received no treatment before operation, 2 were treated with rest in bed, and 1 was treated with bandages and casts. The roentgenograms throughout failed to show any abnormality except for erosion of the cartilage in case 4. In the first case complete excision was attempted, hemorrhage and infection followed, and finally amputation had to be performed. Complete excision was possible in only 1 case, in which the tumor was pedunculated. Biopsy followed by radium or roentgen therapy was carried out in the other 3 cases, with practically complete recovery. The final diagnosis of hemangioma was made and verified by histologic study in the first 4 cases. The signs, symptoms and course made the diagnosis certain in the last case.

REVIEW OF LITERATURE

Twenty-four authentic cases (table 2) of hemangioma of the knee joint, Weaver [1] included a third case, reported by Eve,[2] which in our opinion is not a proved case. A summary of the cases reveals that the age of onset of the symptoms varied from birth to 28 years of age; 85 per cent of the patients were under 16 years of age. However, when final treatment was instituted they varied from 10 to 37 years of age, and 90 per cent were over 16.

The duration of symptoms varied from one to twenty-five years. Trauma (some minor injury) was noted in 60 per cent, while in the

1. Weaver, J. B.: Hemangiomata of the Lower Extremities, with Special Reference to Those of the Knee-Joint Capsule and the Phenomenon of Spontaneous Obliteration, J. Bone & Joint Surg. **20**:731-749 (July) 1938.

2. Eve, F.: Cases of Angioma of the Synovial Membranes and of Muscle, Brit. M. J. **1**:1143-1144, 1903.

TABLE 1.—*Five Personally Observed Cases of Hemangioma of the Knee Joint*

Patient	Date Seen	Sex of Patient	Age at Operation	Duration of Symptoms	Trauma	Pain and Swelling	Intermittent Symptoms	Tenderness	Elastic Spongy Mass	Distensible and Compressible	Pain on Motion	Limitation of Motion	Crepitation	Muscular Atrophy	Limp	Roentgen Examination	Preoperative Diagnosis	Preoperative Treatment	Treatment	Tissues Involved	Hemorrhage at Operation	Result
1. E. E.....*	1915	F	8	7	No	Yes	Yes	....	Yes	....	....	....	....	Yes	....	.....	.....	None	Attempted excision	Synovia	Profuse	Amputation
2. M. W.....	1925	F	12	8	No	Yes	Yes	....	Yes	Yes	Yes	Yes	....	Yes	Yes	No abnormality	.....	Rest in bed	Biopsy; radium therapy	Capsule and synovia	Moderate	Recovery
3. P. M.....	1930	M	13	5	No	Yes	Yes	Yes	....	....	Yes	Yes	....	....	Yes	No abnormality	.....	Rest in bed	Complete excision (pedunculated)	Synovia	None	Recovery
4. M. K.....	1935	F	6	6	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	....	Yes	Slight erosion femur and tibia	Hemangioma	Bandages and cast	Biopsy; roentgen therapy	Synovia	Moderate	Recovery
5. J. T.....	1937	M	18	90 min.	No	Yes	....	....	....	Yes	Yes	....	....	....	Yes	No abnormality	Hemangioma	Aspiration blood	Exploration; roentgen therapy	Synovia	Joint full of blood	Recovery

* When the patient was first seen the roentgenograms showed no abnormality.

other cases there was no history of injury. There were 13 male and 11 female patients. Pain and swelling, whether localized to one part of the joint or to the entire joint and the surrounding bursae, were constant symptoms. The history was that of recurring attacks with usually enough pain on motion to cause a limp. While tenderness was not a constant sign, an elastic, palpable spongy mass, compressible and distensible, disappearing on elevation of the extremity, was present in 70 per cent of cases. Atrophy of muscle was noted in 11 cases.

Most of the patients had been treated previous to diagnosis and operation by means of rest, hot or cold compresses, heat, massage, splints or casts. Eight of the 24 patients had been treated by aspiration of the joint, and in 7 of the 8 cases blood was aspirated. No preoperative diagnosis was made in 9 cases. Tuberculosis of the joint or synovial membrane was the diagnosis in 9 cases, while tumor, tumor of the cartilage, free body in the joint, torn semilunar cartilage, lipoma, syphilis and "encapsulated bloody joint effusion" were diagnoses made in the other cases. In only 1 case was the correct preoperative diagnosis made. Roentgenograms were of little help. Capsular thickening and vague shadows in the joints were seen in many cases. In 2, actual destruction of bone was evident. Treatment in all cases consisted of attempted excision of the tumor. Only in the cases in which a pedunculated, encapsulated tumor or a small synovial or capsular lesion was present was complete excision possible. In 6 of the 24 cases a second operation was necessary to remove the major part of the tumor and to control hemorrhage. Complete excision of the joint was necessary in 1 case, in which the tumor involved the patella, the tibia and the femur. In the majority of cases the involvement was limited to the synovia, the capsule and the subpatellar fat pad, with an occasional spread to the muscles of the lower part of the thigh. At operation the capsule was usually stained from the increase in venous blood. A mass was present, which appeared to be elastic, bluish and often glistening and to be made up of extremely friable, thin-walled vessels. When this mass was punctured, hemorrhage was always profuse and extremely difficult to control. At times the tourniquet and cautery seemed inadequate to keep the patient from bleeding to death during or after the operation, but no patient died, and complete recovery was reported in 11 cases. A good result, with 75 to 90 degrees of motion in flexion, was obtained in 7 cases. In 2 cases both extension and flexion was limited, and in the other there was a solid fusion of the joint. Recurrence was not noted in any case. The pathologic sections revealed hemangioma in every case. The histologic picture was typical of cavernous hemangioma, presenting irregular, blood-filled areas separated by serpentinous spongy thin tissue septums.

TABLE 2.—*Twenty Cases of Hemangioma of the Knee Joint Reported in the Literature*

Author	Sex of Patient	Age at Operation	Duration of Symptoms, Yr.	Trauma	Pain and Swelling	Intermittent Symptoms	Tenderness	Elastic Spongy Mass	Distensible and Compressible	Pain on Motion	Limitation of Motion	Crepitation	Muscular Atrophy	Limp	Roentgen Examination	Preoperative Diagnosis	Preoperative Treatment	Operation	Tissues Involved	Hemorrhage at Operation	Result
Bouchut [14a]	F	3	..	....	....	....	....	Yes	Yes	....	....	....	....	....	.....	.....	Aspirated blood	Died of diarrhea before operation	At autopsy, capsule and medial femoral condyle	.....	Death (diagnosis verified by microscopic study)
Duda [12a]	M	18	4 wks.	....	Yes	....	....	....	Yes	Yes	....	....	....	....	.....	.....	.....	Complete excision	Capsule and synovia	.....	Recovery
Eve [2]	F	15	4	No	Yes	Yes	....	Yes	Yes	Yes	....	....	....	....	.....	.....	None	Partial excision	Capsule and vastus lateralis	Profuse	Recovery
Eve [2]	M	10	5	No	Yes	....	....	Yes	Yes	Yes	Yes	....	Yes	....	.....	Tuberculosis	None	Complete excision	Capsule	None	Recovery
Zesas, D. G.: Deutsche Ztschr. f. Chir. **82**: 267-270, 1906	M	25	1	No	Yes	Yes	....	Yes	Yes	Yes	....	Yes	....	....	.....	Tuberculosis	None	Complete excision	Capsule and synovia	Moderate	Recovery 90° flexion
Reichel, P., and Nauwerck, C.: Arch. f. klin. Chir. **95**: 899-902, 1911	M	18	2	No	Yes	Yes	....	Yes	....	Yes	....	....	....	Yes	Capsular thickening	Tuberculosis or free body	Aspiration; phenol instilled; splint for 8 weeks	Complete excision	Synovia	None	Recovery 75° flexion
Seidener, M.: Dissert., Munich, 1910; Kastner and Calle, 1910	M	37	2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	....	....	....	Yes	Shadows under patella	.....	Aspiration; rest; cast	Partial excision	Fascia, capsule and synovia	Profuse	Recovery
Müller [18]	F	17	2	No	Yes	Yes	....	....	Yes	....	Yes	....	....	....	Essentially irrelevant	Tuberculosis	Bandage and massage	Complete excision	Capsule	Apparently none	Recovery
Oeser [11]	M	33	20	Yes	Yes	Yes	....	....	....	Yes	Yes	....	Yes	....	.....	.....	Periods of rest	Complete excision (pedunculated)	Synovia	Profuse	Recovery 90° flexion
Osgood [12b]	F	26	8	Yes	Yes	Yes	Yes	Yes	....	Yes	Yes	....	Yes	....	Atrophy of bone	Gumma, tumor, lipoma or tuberculosis	Rest; cast, 6 weeks	Complete excision	Synovia and infrapatellar fat pad	None	Recovery
Hilgenberg, F. C.: Beitr. z. klin. Chir. **123**: 645-654, 1921	M	19	5	Yes	Yes	Yes	....	Yes	Yes	Yes	....	....	Yes	Yes	Diffuse shadows in joint space	Tuberculosis	Rest 4 weeks	Complete excision	Capsule; synovia; cartilage of lateral tibial condyle	Profuse	Partial recovery; 90° flexion
Haas [10]	M	23 30	25	No	Yes	Yes	Yes	....	Yes	Yes	....	Yes	Yes	Yes	Destruction medial tibial condyle	.....	Casts for first 5 years	2 operations; excision; arthrodesis	Capsule; tibia; femur; patella	Profuse	Solid fusion; no recurrence
Haas [10]	F	17	17	No	Yes	Yes	Yes	Yes	Yes	Yes	....	....	Yes	Yes	No abnor-	Heman-	Rest	2 opera-	Synovia	Mild	Recovery

															space				of lateral tibial condyle		
Haas [10]	M	23 30	25	No	Yes	Yes	Yes	....	Yes	Yes	....	Yes	Yes	Yes	Destruction medial tibial condyle	.....	Casts for first 5 years	2 operations; excision; arthrodesis	Capsule; tibia; femur; patella	Profuse	Solid fusion; no recurrence
Haas [10]	F	17 20	17	No	Yes	Yes	Yes	Yes	Yes	Yes	....	....	Yes	Yes	No abnormality	Hemangioma	Rest	2 operations; complete excision	Synovia	Mild	Recovery
O'Ferrall [14b]	M	19	6	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	....	Yes	....	No abnormality	Cartilage	Aspiration of blood; ace bandage	Complete excision	Capsule and synovia	Profuse; 2 operations to control bleeding	25° permanent flexion deformity; 105° motion
O'Ferrall [14b]	F	20	18	Yes	Yes	Yes	....	Yes	Yes	Yes	Yes	....	....	Yes	No abnormality	Tumor of cartilage or tuberculosis	Cast and rest	2 operations; partial excision	Synovia and periosteum of femur	Profuse; controlled with pressure	Recovery; 105° flexion
O'Ferrall [14b]	F	24	19	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Shadows under patella	Lipoma	Ice cap and rest	Complete excision	Infrapatellar fat pad	None	Recovery
Bertelsmann [20]	F	27	12	Yes	Yes	Yes	Yes	Yes	....	Yes	....	Yes	Yes	Yes	Thickened periosteum end of femur	Tuberculosis	Heat; diathermy; rest	Complete excision	Patella, articular surface and capsule	None	Recovery
Eggers [4a]	F	18	8	No	Yes	Yes	Yes	....	Yes	....	Yes	Yes	Yes	....	No abnormality	Encapsulated effusion	Aspirated blood	Complete excision	Synovia; capsule; femur	Profuse; controlled with pressure	Recovery
Lauwers, G. B.: Nederl. tijdschr. v. geneesk. **2:** 6384 (Dec. 29) 1928	F	30	2	Yes	Yes	....	....	....	Yes	....	....	....	Yes	Yes	No abnormality	.....	Compression bandage and massage, 2 years	Partial excision	Synovia; entire crural space	Profuse	Symptom free for 1 year after operation
Venezian, E.: Chir. d. org. di movimento **14:** 266-284 (Oct.) 1929	M	5	18 mo.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	....	Yes	No abnormality	.....	Aspiration 1 cc. blood	Partial	Synovia and capsule	Profuse	Marked limitation of motion
Bastos, E. S.: Bol. Soc. de med. e. cir., São Paulo **15:** 475-478 (Feb.-March) 1932	M	30	20	No	Yes	Yes	....	Yes	Yes	....	....	....	Yes	Yes	No abnormality	.....	Heat, massage and casts for 10 years	Complete excision	Synovia	None	Recovery; 90° flexion
Masmonteil, F.: Bull. et mem. Soc. d. chirurgiens de Paris **28:** 109-116 (March 6) 1936	M	18	10	Yes	Yes	Yes	Yes	....	....	Yes	....	....	Yes	Yes	Atrophy of bone	Tuberculosis, syphilis or internal cartilage	Bed rest for tuberculosis	Complete excision	Capsule; 2 cm. lobule	None	Recovery
Mizuno, I.: Zentralbl. f. Chir. **64:** 353-356 (Feb. 6) 1937	M	29	17	Yes	Yes	Yes	..:.	Yes	Yes	Yes	....	Yes	Yes	....	Shadows above patella and phleboliths	Tumor	Aspiration of blood; rest	Complete excision	Synovia and capsule	Profuse	Recovery 1 month later
Weaver [1]	F	15	10	Yes	Yes	Yes	Yes	....	....	Yes	Yes	....	Yes	....	.....	.....	Plaster cast	Complete excision	Capsule; small encapsulated tumor	.....	Recovery

CAUSE

The cause of hemangioma is still much discussed. The lesion is generally considered to be either congenital or traumatic. In about half the cases the patients report some minor injury, such as bumping the knee on closing a drawer or falling and striking the knee. However, in many cases no history of injury is obtained. The relatively early appearance of the tumor and its close association with telangiectasis and various other types of hemangioma as found in the skin,[3] muscle,[4] spine,[5] tendon sheaths,[6] and other structures of the body suggests a congenital origin. Jenkins and Delaney[7] in discussing various types of hemangioma stated:

> It seems fair to assume as a working hypothesis that none of these vascular tumors are true growths and are due to faulty development, and that the variations encountered are due to the stage of vascular development in which deviation from the normal occurred.

Cases have been reported in which a cavernous hemangioma following trauma became malignant, metastases occurring in the skin of the head and in the skull.[8] So far, no malignant change in a hemangioma of the knee joint has been reported, and no such change, as far as can be determined, has occurred in any of our cases. The fact that hemangioma is seen most commonly in those parts[9] which in embryonic life correspond to fissures, the fact that a number of these articular tumors have arisen from the bones above and below the joint, the fact that the onset occurs before the patient begins to walk much or is able to injure the joint severely and the fact that the tumor is composed of immaturely formed blood vessels lead one strongly toward belief in a congenital origin.[10]

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3. Roesler, H.: Hemangioma: Some Observations on the Results of Radiation Therapy, Am. J. Roentgenol. **27**:249-256 (Feb.) 1932.

4. (*a*) Eggers, H.: Zirkumskripte kavernöse Hämangiome der Kniegelenkskapsel, Zentralbl. f. Chir. **54**:1409-1411 (June 4) 1927. (*b*) Thomas, H. B.: Angiomas of the Skeletal Muscle: Combined Operative and Radiation Therapy; Two Case Reports, Am. J. Surg. **31**:354-360 (Feb.) 1936.

5. Heaney, F. S., and Whitaker, P. H.: Hemangioma of the Spine, Brit. M. J. **2**:775-776 (Oct. 28) 1933.

6. Burman, M. S., and Milgram, J. E.: Hemangioma of the Tendon and Tendon Sheath, Surg., Gynec. & Obst. **50**:397-406 (Feb.) 1930.

7. Jenkins, H. P., and Delaney, P. A.: Benign Angiomatous Tumors of the Skeletal Muscles, Surg., Gynec. & Obst. **55**:464-480 (Oct.) 1932.

8. Downing, J. G., and Mallory, G. K.: Cavernous Hemangioma and Trauma: Report of a Case, Arch. Dermat. & Syph. **22**:414-422 (Sept.) 1930.

9. Davis, J. S., and Wilgis, H. E.: Treatment of Hemangiomata by Excision, South. M. J. **27**:283-290 (April) 1934.

10. Haas, A.: Ueber Gefässtumoren der Kniegelenkkapsel, Deutsche Ztschr f. Chir. **173**:130-141, 1922.

PATHOLOGIC PICTURE

This tumor has been studied minutely for its individual pathologic picture and is easily recognized as a pathologic entity. The capsule shows villous formation with deposition of blood pigment. The tumor is composed grossly of large masses of bluish venous sinuses interlaced on themselves, the individual sinus varying from the size of a small venule to more than 1 cm. in diameter. These are separated from each other by thin-walled, friable, partly fatty and partly connective tissue.[11] Microscopically[12] they are thin-walled vascular areas, varying greatly in size and showing much connective tissue cell proliferation. Because they do not carry the normal histologic coats of the true vessel walls, they cannot be thought to be varicose vessels or aneurysms. They are apparently neoplastic outgrowths of vascular tissue. The irregular spaces are lined with epithelium, the outer wall of the vessel usually being absent. A considerable amount of loose connective tissue containing blood vessels is seen all through the mass. Blood cells can be seen pushing their way between the lines of endothelial cells going to form new channels.

SYMPTOMS

All the cases present the same striking cardinal signs. They are pain and intermittent swelling since early life, with slight limitation on extremes of motion. The swelling, which is present about the patella, disappears on elevation of the extremity. There is no marked increase in local heat and usually no cutaneous discoloration. The swelling is boggy, almost fluctuant. Occasionally there is a clicking sensation in the knee. Pain is never constant but is occasionally associated with the swelling. Motion of the joint is usually free and painless.

EXAMINATION AND DIAGNOSIS

Tuberculin and Wassermann tests give negative results, and abnormal changes in the leukocyte count are not found. Roentgen examination generally shows only the swollen outlines of the joint; it discloses no changes in bone except occasionally atrophy of disuse or a slight erosion. Several authors[13] have reported the value of the appearance of phlebo-

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11. Oeser, R.: Zur Kenntnis der Gutartigen Gelenkkapselgeschwülste, Beitr. z. klin. Chir. **107**:65-75, 1917.

12. (*a*) Duda, O.: Ueber einen Fall von Angiom der Kniegelenkkapsel, Greifswald, J. Abel, 1894. (*b*) Osgood, R. B.: Angioma of the Knee Joint, S. Clin. North America **1**:681 (June) 1921. Eve.[2] Haas.[10]

13. Teller, W. H.; Solis-Cohen, L., and Levine, S.: Cavernous Hemangioma of the Leg, Radiology **22**:369-371 (March) 1934. Davis, J. S., and Kitlowski, E. A.: Primary Intramuscular Hemangiomas of Striated Muscle, Arch. Surg. **20**:39-86 (Jan.) 1930. Eve.[2] Jenkins and Delaney.[7] Davis and Wilgis.[9]

liths in the roentgenogram not only as a diagnostic point but as a means of operative approach to the feeding vessels. Aspiration of the joint has been recommended and should be carried out in order to make the diagnosis certain.[14] Visualization by radio-opaque substances offers a possible diagnostic approach.[15]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is important. Hemangioma should not be confused with tuberculosis of the knee. Note should be taken of the intermittent character of the swelling, the pain and the limp and also of the gradual increase in size of the swelling and of the doughy, knotty feeling on either side of the patella. Also, if the condition is hemangioma the mass is reduced if the extremity is raised, the Mantoux test gives a negative result and roentgen examination does not reveal the signs of tuberculosis. Syphilis of the joint may be ruled out by a negative reaction to the Wassermann test and absence of the other signs of congenital syphilis. Syphilis does not present a compressible mass or free blood in the joint. Traumatic effusion usually causes a more symmetric swelling and outlines the bursae. In the presence of such effusion there is true fluctuation and may be change in surface temperature and greater pain on motion. The swelling is noncompressible, and serous or serosanguineous fluid may be aspirated. The history of an occasional locking or clicking sensation may lead to the diagnosis of injury to the semilunar cartilage, but the feeling of the mass about the patella, the history of long duration and the change in size of the mass on elevation of the leg will make the diagnosis clear. An infectious lesion shows more pain on motion, increase in local heat, extremely acute recurrence of symptoms, persistent swelling and possible involvement of other joints or roentgenographic changes in the bones. Xanthomatous villous arthritis of the knee (a rare condition) will confuse the diagnois more than any other condition. However, a chemical study of the cholesterol content of the blood and synovial fluid will aid materially in differentiating the two conditions.

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14. (*a*) Bouchut, E.: Tumeur érectile de l'articulation du genou, Gaz. d. hôp. **29**:379, 1856. (*b*) O'Ferrall, J. T.: Hemangiomas of the Knee Joint, J. A. M. A. **85**:505-508 (Aug. 15) 1925. Osgood.[12b] Roesler.[3]

15. (*a*) Patey, D. H.; Tatham, R. C., and Nicholas, F. G.: The Use of X-Rays in the Investigation of Varicose Veins, Lancet **2**:1309-1311 (Dec. 9) 1933. (*b*) Otell, L. S.; Coe, F. O., and Hedley, O. F.: Thorotrast Arteriography and Veinography, M. Ann. District of Columbia **2**:153-156 (July) 1933. (*c*) Allen, E. V., and Barker, W. W.: Roentgenologic Visualization of the Veins of the Extremities: Preliminary Description of a Method, Proc. Staff Meet., Mayo Clin. **9**:71-74 (Jan. 31) 1934.

TREATMENT

Since this lesion appears so early in life, it would seem that the earlier the treatment the more satisfactory the result. The tumor may take one of three forms: diffuse, pedunculated or encapsulated. In any case it will remain stationary, regress in size or grow very rapidly at any time or age of the patient, seemingly regardless of the presence or absence of competent cause.[16]

The type of treatment is a matter of choice. Hemangioma in general has been treated by excision or by conversion of the mass into scar tissue, solid carbon dioxide, sclerosing solutions, roentgen and/or radium radiation,[4b] or the cautery being used. In general, the type of tumor indicates the type of treatment. For hemangioma of the knee joint, treatment by excision has been carried out in almost all the cases reported. This procedure is excellent for the small impinging hemangioma [12b] or for the occasional pedunculated hemangioma,[17] which can be easily stripped away from the surrounding tissue, tied and removed. For the large wormlike sinus formation leading far up into the muscle or down into the periosteum, cartilage or bone [18] the chances of complete excision are not great. Each writer has reported the difficulty of controlling hemorrhage from the bone and the extensively involved capsule. Some surgeons have used many ligatures; others have used pads of fat over the bleeding vessels, and still others have found a second operation necessary to control hemorrhage.[10] Complete excision is a difficult matter,[19] and cases of recurrence have been reported. In 1, removal of the ends of the femur and tibia and fusion of the joint were necessary [10] both to control hemorrhage and to insure complete excision and relief of symptoms. Infection followed by gangrene and amputation was the result in 1 case. However, many cases have been reported in which complete removal of the hemangioma was followed by healing per primam intentionem and by complete relief of symptoms. These cases demonstrate the guarded prognosis as to the range of motion that will be obtained after operation and as to the freedom from symptoms.[19] There is no doubt that a large hemangioma of muscle, skin, tendon and subcutaneous tissue can be removed surgically with good results.[8] Surgical treatment in our first case resulted finally in the loss of the extremity; in the third the lesion was pedunculated and could easily be removed; in the second case a specimen was taken for biopsy and subse-

16. Traub, E. F.: Should Vascular Nevi Be Treated? Arch. Pediat. **50**:272-278 (April) 1933.

17. Oeser.[11] Jenkins and Delaney.[7]

18. Müller, W.: Beiträge zur Kenntnis des Lymphangioms, Beitr. z. klin. Chir. **84**:511-536, 1913. Duda.[12a] Oeser.[11] Osgood.[12b]

19. Osgood.[12b] Haas.[10]

quent radium treatment given, and in the fourth and fifth cases exploration only was attempted and the patient referred for roentgen therapy. In our third case the lesion apparently healed completely, and the patient has been free from symptoms for years after treatment, without clinical signs of recurrence of the tumor. Owing to the operative dangers and the uncertainty of the operative results, complete removal was not attempted in our 3 cases,[20] roentgen therapy being preferred. This was first suggested in 1925 but was not attempted prior to the cases reported in this paper so far as we know.

CONCLUSIONS

The cardinal points in the diagnosis of hemangioma are (1) intermittent pain and swelling present since early life, with or without history of trauma, (2) no pain on motion, (3) slight limitation of motion, (4) the presence of another hemangioma anywhere on the body, (5) reduction in size of the swelling on elevation of the extremity, (6) negative results from laboratory and roentgen examinations and (7) aspiration of blood from the joint.

For the small or pedunculated tumor the treatment is complete excision. Owing to the almost uncontrollable hemorrhage, with the danger of loss of function of the joint, amputation or infection followed by septicemia we believe that a larger nonpedunculated tumor is more satisfactorily treated by rest and by radium or roentgen therapy.

20. Bertelsmann, R.: Zirkumskripte kavernöse Hämangiome der Kniegelenkskapsel, Zentralbl. f. Chir. **54**:710-711 (March 19) 1927. Patey and others.[17a]

ATRESIA ANI URETHRALIS

REPORT OF A CASE

L. ALBERT THUNIG, M.D.
BROOKLYN

"Congenital malformations of the rectum and anus are rare. Various authors give the incidence of 1 in 5,000 to 1 in 10,000. No two lesions seem to be identical in their physical characteristics, though fundamentally they are all variations of a known embryonic plan of development." [1]

These figures refer to all types of anal and rectal anomalies. The incidence of the particular anomaly to be described in this paper is considerably smaller, as it comprises less than 30 per cent of the incidence of all anomalies of the rectum and anus. That this is so and that the operative mortality rate is high and the failure to accomplish a satisfactory result common are borne out in statements quoted by Young.[2]

Cripps [3] collected 100 cases of imperforate anus. There were 13 male patients, of whom 10 died. Autopsy was performed on these. Six had fistulas between the prostate and the rectum; 4, had fistulas between the rectum and the bladder.

Keith [4] among 114 cases found 33 in which there was a communication between the rectum and the urethra.

Quinland [5] reported 27 cases of imperforate anus; there were 7 male patients, 6 of whom had urethrorectal fistulas.

Barney [6] among 375 cases found 94 in which the rectum communicated with some part of the urinary tract.

Ladd and Gross [7] among 162 anomalies of the anus and rectum found only 9 in which the rectum communicated with the urethra.

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1. David, V. C.: Surgery of the Rectum and Anus, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1930, vol. 7, chap. 6, p. 1.

2. Young, H.: Congenital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, Williams & Wilkins Company, 1937, pp. 580-583.

3. Cripps: St. Barth. Hosp. Rep. **18**:65, 1882.

4. Keith, A.: Brit. M. J. **2**:1736, 1908.

5. Quinland, W. S.: Boston M. & S. J. **187**:870, 1922.

6. Barney, J. D.: Tr. Am. A. Genito-Urin. Surgeons **21**:393, 1928.

7. Ladd, W. E., and Gross, R. E.: Am. J. Surg. **23**:167, 1934.

OPERATIVE PROCEDURES AND RESULTS

Colostomy was proposed by Littre in 1710.[5] Bell of England in 1787 made the first perineal dissection.[6] Campbell of the United States in 1790 performed the first successful perineal operation.[6] In 1828 Dieffenbach proposed the perineal operation.[9]

In a series of 55 cases of atresia ani urethralis occurring in males, reported by Parin,[8] the immediate operative mortality was 32 per cent. In only 1 case was a perineal rectal plastic operation with attempt to close the urethral fistula performed; the patient in this case died. In 4 cases perineal rectal plastic operations were performed with secondary closure of the urethral fistula; there was 1 death.

In 9 cases of atresia ani urethralis reported by Ladd and Gross [7] the combined operation of perineal rectal plastic procedure and closure of the urethral fistula in one stage was performed on 7 patients; 4 died, 3 recovered, and there was only 1 cure. In 2 cases the urethral fistula was operated on when the patient was 5 years old, with 1 cure and 1 failure. As a result of their experience Ladd and Gross have decided that the method of choice is immediate colostomy with a perineal plastic operation when the patient is 8 or 9 years old.

Young [9] stated that two schools have developed: (1) physicians favoring a primary colostomy with secondary perineal repair, and (2) physicians favoring an immediate perineal plastic operation.

I feel justified in placing my case on record in view of the following facts:

1. The anomaly to be reported is rare.

2. The operation was undertaken forty-eight hours after the child was born.

3. The procedure was a primary perineal plastic operation with attempt to obliterate the fistula between the urethra and the rectum.

4. The operation resulted in recovery with a very good anus, and good function was apparent during eleven years of observation.

I feel justified, furthermore, in devoting space to a description of the embryonic background of this anomaly and a correlation between the embryologic facts and the anatomic conditions found at operation in addition to that devoted to facts evidenced by function, for the reason that I believe that only by such detailed attention to these anomalies will physicians eventually be able to discard conjecture and come to fairly accurate conclusions as regards the factors of developmental error producing these interesting anomalies.

8. Parin, B.: Arch. f. klin. Chir. **166**:386, 1931.
9. Young,[2] p. 581.

REPORT OF CASE

R. F., a boy born Sept. 2, 1925, was an apparently robust baby weighing about 8 pounds (3,628 Gm.). He had normal male genitals with testes in the scrotum and a normal attachment of the umbilical cord (also, a normal umbilicus after separation of the cord). There was some vomiting during the second day; the baby voided urine normally but had no stool. When the child was about 40 hours old, the nurse, in starting to give an enema, found no evidence of an anus and also noticed that the boy was passing very dark urine. Examination showed that the boy was passing meconium through the penis, and inspection of the anal area showed a perfectly flat surface without even a dimple where the anus should have been. The baby was removed to the Swedish Hospital.

An F. 8 metal Gouley tunneled catheter was introduced, with the following results: 1. When the catheter was passed in the usual manner and the stilet withdrawn, almost clear urine was obtained (fig. 1). 2. When the catheter was passed with easy pressure of the curve of the instrument on the perineum,

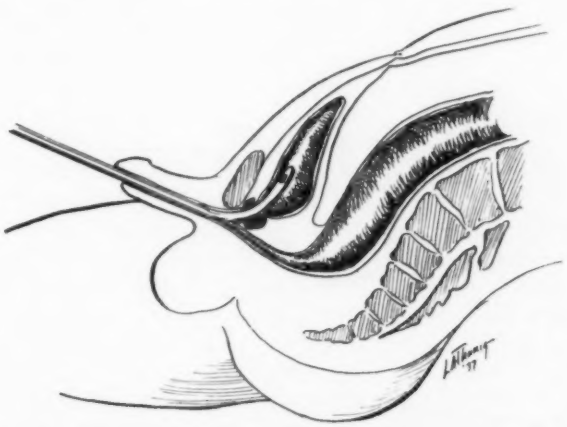

Fig. 1.—Semidiagrammatic drawing of the anomaly with an F. 8 Gouley tunneled catheter in position, the tip being in the bladder.

the tip pointing toward the sacrum, meconium came through the catheter on withdrawal of the stilet (fig. 2). 3. It was found that this procedure could be repeated at will with the greatest ease.

The three facts just mentioned established the following conclusions:

1. There was a communication between the urinary tract and the rectum.

2. This communication was between the urethra and the rectum, for it is obvious that if the opening had been in the bladder it could not have been found at will.

3. The communication was with the penile portion of the urethra. The ease of the procedure and the position of the metal catheter verified this fact, for if the point of communication had been in the membranous or the prostatic portion of the urethra the technic of passing the catheter would have been different, and the procedure certainly would not have been so easy.

4. There was not merely an opening but a definite tract between the penile portion of the urethra and the blind end of the rectum, and the rectum was not

attached immediately to the proximal end of the penile portion of the urethra. The depth to which the catheter had to be passed to obtain meconium showed that the rectal pouch was some distance from the proximal end of the urethra and was close to the sacrum. (This was confirmed at operation.) (Figure 2 is drawn to show the position of the catheter when it was being passed and not the depth to which it could be passed. Had I drawn the catheter well into the rectal pouch, the point which I wished to demonstrate, i. e., the technic of passing, would have been lost.)

5. Some part of the rectum was present moderately low in the pelvis.

6. The bladder, which functioned apparently normally, was not involved in the anomaly.

With the preoperative diagnosis well established, operation was performed on September 4, the boy being about 48 hours old. Owing to the fact that this baby was returned home immediately after operation, the records of the Swedish Hospital show only the schedule for the operation; all facts given here are from my private records.

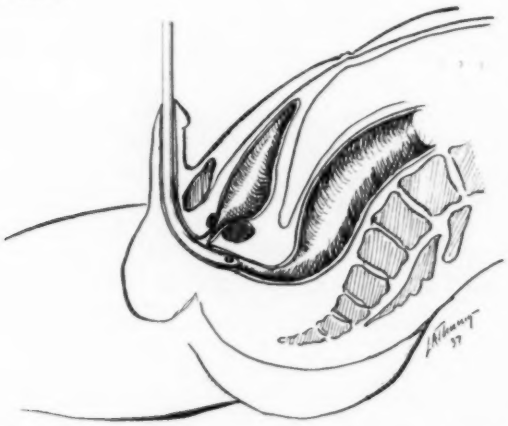

Fig. 2.—Semidiagrammatic drawing of the anomaly with an F. 8 Gouley tunneled catheter in position, the tip being in the tract between the rectum and the urethra. The catheter is shown in this position to demonstrate the position of the instrument which is necessary to avoid the membranous portion of the urethra and to assure entrance into the rectum.

Operation.—The operation was performed without anesthesia. The baby was held in the lithotomy position with the thighs flexed on the abdomen and the scrotum well forward. A metal F. 8 Gouley tunneled catheter was passed through the penile portion of the urethra and fistulous tract into the rectal pouch. This instrument was held steadily in the midline by Dr. J. Borgia. A median perineal incision was made from just behind the scrotal perineal junction to within a short distance of the coccyx. There was no external evidence of a sphincter muscle, but I believed that if the muscle were present its fibers might be split by keeping directly in the midline. After the cutaneous incision had been made, no attempt was made to find the sphincter, but midline dissection was done. Sharp and blunt dissection was carried slowly upward, the curve of the sacrum being followed and the catheter guide being avoided to prevent vesical or urethral damage. At a distance of 1½ to 2 inches (3.7 to 5 cm.) above the perineal level the dark rectal pouch was seen. Exploratory aspiration was

made with a fine hypodermic needle, and meconium was obtained. Two heavy black silk sutures were then placed in the walls of the rectal pouch as guides and tractors. By blunt dissection this pouch was mobilized from the sacrum, care being taken to avoid the peritoneum anteriorly. Without difficulty the pouch was freed so that without tension it could be delivered well below the perineal level. The tract between the rectum and the bladder was ligated with two ligatures, the metal catheter having been withdrawn some time previously, close to the rectal pouch to avoid "Y-ing" the urethra and ligating the same; it was then cut between the ligatures. The rectal pouch was now drawn about 1 inch (2.5 cm.) below the perineal level and was opened with an anteroposterior median incision which gave two fairly large lateral flaps. This incision was followed by a most copious meconium stool. No attempt was made to obtain a cutaneous rectal suture line for the reason that this might be followed by rectal retraction with serious or fatal consequences. Instead, the lateral flaps were brought well over the line of the cutaneous incision on each side and sutured with several heavy black silk sutures to the unbroken skin. The idea underlying this procedure was that the raw rectal surface would come into contact with the whole thickness of incised skin, connective tissue and sphincter muscle (if this was present); it would furthermore allow for rectal retraction, which could easily take place by cutting through of the silk sutures and still give some rectal edge outside the pelvis. It would also allow for some sloughing of the rectal edge without interference in cutaneous rectal union. The remaining ends of the perineal cutaneous incision were then brought together with interrupted sutures. The operation took about one and one-quarter hours.

The immediate postoperative course was uneventful. There was no infection. The child nursed well; there was no more vomiting and the bowels functioned. The redundant rectal tissue retracted somewhat and sloughed somewhat, and a very presentable anus developed. At times the skin became red and irritated, but function was excellent. Control at this time was difficult to interpret. For the first few months the parents kept the anus well dilated by daily passage of a 4LF rubber rectal bougie, and I frequently examined and dilated it with my finger.

For two years continued improvement took place, with apparently good rectal and excellent vesical control. At the cutaneous rectal edge, however, a small urinary fistula developed, through which with the act of urination some urine occasionally leaked, and very rarely a trace of feces appeared in the urine by way of the urethra. The follow-up demonstrated that the presence of this trace of feces was not due to any rectal-urinary fistula but to the forcing of feces into the open end of the penile portion of the urethra at the perineal-anal junction during defecation or cleansing; this fecal contamination was then washed out in the act of urination. By Dec. 3, 1927, the boy was having fair-sized, formed stools under control; feces appeared in the voided urine only when a saline laxative was given. By September 1929 control of the bowel was excellent; control of the bladder was perfect, with only an occasional perineal urinary leak with voiding. By March 1932 there were no traces of feces in the voided urine and only occasionally was there a urinary leak on urination. This boy was last seen Jan. 6, 1936. He was having fair-sized, well controlled formed stools with absolutely no rectal leakage unless he had been given a saline laxative, in which case the leakage was only slight. He still had a small urethral-perineal fistula, which opened near the anus, but there was no more contamination of the urine with traces of feces.

The reader will probably wonder why I have not reported the physical findings with the follow-up reports. I was unable to make rectal examinations even

though I was particularly anxious to do so; I had to depend entirely on the record of function and the size of the stools. It may be difficult to believe that the simple process of rectal examination should for any reason be withheld, but it was, for the following reasons: First, this boy was an excellent example of a spoiled child, as was his elder brother, through whose intolerable behavior during an illness in February 1936 my connection with this interesting case was severed. Second, the boy had a series of physical mishaps. In July 1927 he had mild ileocolitis; in June 1928 he had measles; in December he had lobar pneumonia; in January 1929 he had a severe infection of the upper part of the respiratory tract, with bilateral purulent otitis media; in January 1930 he had acute polyarthritis with early severe endocarditis and pulmonary infarct; in February he had recurrent otitis media; in March he had recurrent low grade arthritis with exacerbation of the endocarditis and severe decompensation, and in the same month he had severe chorea with increased endocarditis and decompensation, which made the outcome look very dubious until June. At the first recession of his trouble his tonsils were removed (in June). From June 1930 until January 1936 he had no more acute diseases but suffered with numerous attacks of decompensation. His heart was hugely dilated and hypertrophied, actually causing deformity of the left side of the chest. The liver was large and congested, with variable edema; in short, there was a chronic cardiac valvular lesion which might be expected to make a semi-invalid of the boy for the rest of his life. This series of infections superimposed on an inherited neurotic makeup and the indulgent attitude of the parents toward the boy will, I hope, make it clear that my failure to make rectal examinations was due to circumstances over which I had no control. As a result of his inheritance, environment and physical misfortunes this 11 year boy became absolutely unmanageable in the presence of a physician. At the time of writing he attends a special class for children with cardiac disease and gets along well, his anal condition causing him no annoyance whatever and the occasional urinary leak only slight annoyance, none if he sits down when urinating, to which he seriously objects. In view of the slight inconvenience of this perineal urethral fistula and of the fact that there is no contamination of the urinary tract with feces I advised the parents that it would be best to wait until the boy's general health was better and he had grown before attempting to correct this condition.

Summary.—This was a typical case of atresia ani urethralis or imperforate anus with communication between bowel and urethra, as it is now termed. In my opinion: "congenital absence of the anus with a persistent cloacal duct" is a better name, as both of the previous names predicate the presence of an anus, whereas in this case no anus was present. The term persistent cloacal duct (as will be shown later in this paper) both defines the anomaly and gives its origin.

The case was one in which forty-eight hours after birth a primary perineal rectal plastic operation was undertaken, which resulted in a functioning anus with almost total sphincter control and no tendency to stricture for at least eleven years. There was at no time any difficulty in emptying the bladder or controlling the flow.

The tract between the rectum and the urethra was severed, but at the end of eleven years a small fistula was present between the proximal end of the penile portion of the urethra and the perineum, just in front of the anus. This leaked slightly during urination only. Because the discomfort caused by this fistula was moderate and because the boy's general condition was poor, postponement of operation to correct the fistula to a later period was advised.

In addition to an unusual congenital anomaly operated on with good results the report presents eleven years of the medical history of a most unfortunate boy.

EMBRYOLOGY

In the following section the paragraphs are numbered so that quick reference may be made to them when desired.

1. In discussing the embryologic background I desire to bring forward those facts which relate particularly to the anomaly just presented, and in order to prevent confusion I shall avoid mentioning any association that these facts may have with closely related anomalies. It is my opinion that in attempting to point out with even a semblance of accuracy the factor or factors of developmental error leading to an anomaly it is essential to show not only the actual factor or factors of error but also to limit the cause of the anomaly to the suspected factors by demonstrating the absence of developmental error in organs or structures closely associated in embryonic life with the anomalous organs or structures. For that reason I shall attempt to show not only the actual developmental error but also the development of those anatomic parts which were found to be normal at birth but which were intimately associated with the anomalous parts in embryonic growth.

2. Before entering into the discussion I should like to explain my use of the words "modified copy," used frequently in the legends for the illustrations appearing in this paper. In figures 3 and 4 I have left out those parts of the original which have no bearing on the subject. In figure 14 *A* I have left out several parts already shown in figure 11, which have served their purpose. In all other instances in which drawings are not originals I have tried faithfully to copy the original; I have not made any anatomic changes but have modified my copy in the technic of artistic presentation only.

3. In order that the reader may associate the size of the embryo with the period of development, the following tabulation is quoted from Keith.[10]

Weeks	Millimeters
3	0.5
4	2.5
5	5.5
6	11.0
7	17.0
8	25.0

4. Figure 3 represents an embryo of 1.7 mm. The embryo proper is almost straight, and the yolk sac is proportionately very large with two early outgrowths from the yolk sac into the embryo, one at the

10. Keith, A.: Human Embryology and Morphology, ed. 5, Baltimore, William Wood & Company, 1933, p. 62.

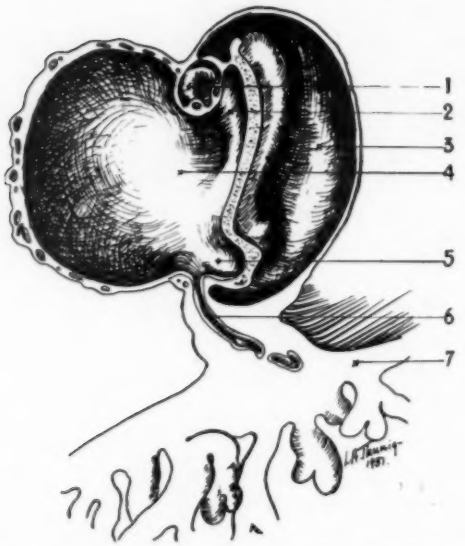

Fig. 3.—Drawing of a 1.7 mm. embryo: a modified copy of an illustration in Cullen, T. S.: The Umbilicus and Its Diseases, Philadelphia, W. B. Saunders Company, 1916, p. 2. *1*, heart; *2*, foregut; *3*, amniotic cavity; *4*, yolk sac; *5*, hindgut; *6*, allontois in body stalk; *7*, chorion.

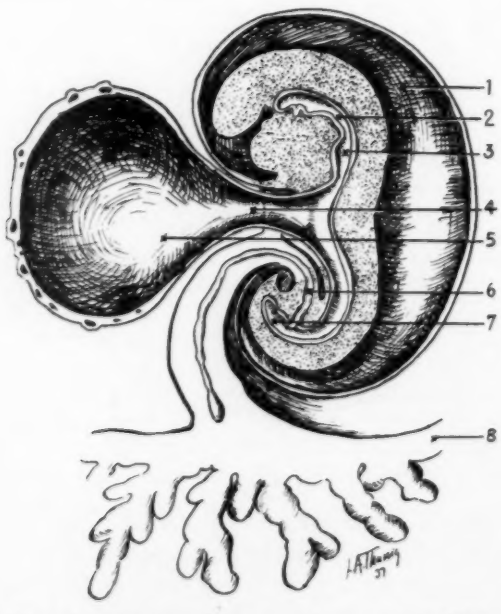

Fig. 4.—Drawing of a 2.5 mm. human embryo: a modified copy of an illustration in Cullen, T. S.: The Umbilicus and Its Diseases, Philadelphia, W. B. Saunders Company, p. 3. *1*, amniotic cavity; *2*, esophagus; *3*, stomach; *4*, omphalomesenteric or vitelline duct; *5*, yolk sac; *6*, allantois; *7*, cloaca; *8*, chorion.

cephalic and one at the caudal end; these become the foregut and the hindgut respectively. Even at this early stage the allantois is present, extending from the yolk sac near the hindgut into the body stem toward the chorion. As a matter of fact, the allantois has been demonstrated in embryos even before the hindgut or foregut could be demonstrated.[11]

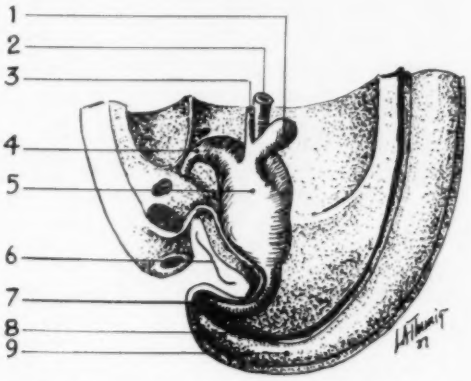

Fig. 5.—Model of a 6.5 mm. human embryo: (modified copy of an illustration in Bailey and Miller[16] [p. 370]): *1*, kidney bud or ureteral bud; *2*, hindgut; *3*, mesonephric or wolffian duct; *4*, urachus; *5*, cloaca; *6*, cloacal membrane; *7*, caudal gut; *8*, notochord; *9*, neural tube.

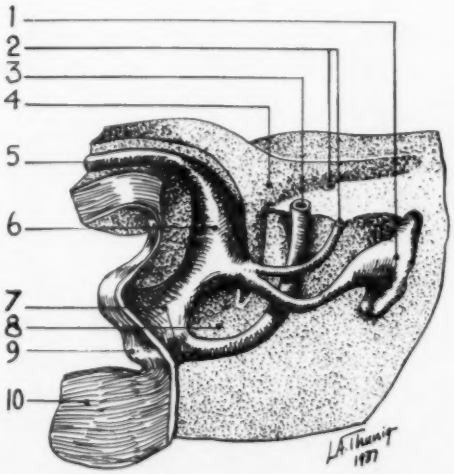

Fig. 6.—Reconstruction of the caudal end of a 11.5 mm. human embryo: (modified copy of an illustration in Bailey and Miller[16] [p. 372]): *1*, primitive renal pelvis; *2*, mesonephric or wolffian ducts; *3*, rectum; *4*, coelum; *5*, urachus; *6*, bladder; *7*, cloaca (undivided portion); *8*, site of urorectal fold; *9*, cloacal membrane; *10*, tail.

11. Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, pp. 293-294.

The allantois [12] is carried along with the hindgut and empties into the terminal part of the hindgut or cloaca (fig. 4).

5. In the 4.9 mm. embryo the cloaca is elongated anteroposteriorly and the wolffian (primary excretory or mesonephric) ducts empty into its ventral portion.[13] In figure 5 the cloaca is shown in an embryo of 6.5 mm., and in addition to the wolffian ducts the kidney buds or, according to Keibel and Mall, the ureteral buds, are present.[14] At this period the wolffian ducts enter the ventral portion of the cloaca laterally. Between the 5.3 mm. stage and the time the embryo has reached 15.5 mm. the cloaca is divided into two parts by a fold of tissue (fig. 6) known as the urorectal fold.[15] There is some difference of opinion as to the formation of the urorectal fold and since the anomaly under discussion depends largely on the division of the cloaca I have chosen to dwell long enough on this particular point to demonstrate at least two of the commonly accepted and outstanding views. Bailey and Miller [16] stated the opinion that the urorectal fold is formed by paired folds arising on the lateral walls of the cloaca at its cephalic end, which spread downward and unite to form a single septum which divides the cloaca (figs. 7 and 8) into an anterior part, the urogenital sinus, and a posterior smaller part, the rectum.[16] Keibel and Mall described the urorectal fold as an unpaired fold starting in saddle fashion at the cephalic end of the cloaca, between the allantois and the hindgut, and gradually projecting downward, growing somewhat faster at the lateral walls than at the center, thus giving the free lower edge of the fold a curved rather than a straight edge. They maintained this view on the ground that no raphe is formed as would be the case if two lateral folds came together and fused centrally and also on the ground that Keith [10] in 1896 described a groove or slight ridge on the outer surface of the cloaca (fig. 9) corresponding with the line along which this unpaired fold grew internally.[15] These authors also stated that epithelial differentiation between the rectum and the ventral remains of the cloaca (fig. 10) takes place before the actual division of the cloaca.[15] About the time the embryo has reached 11 to 12.5 mm. the urorectal fold (figs. 9 *B* and 9 *C*) has divided the cloaca so far caudally [17] that only a duct remains between the rectum and the urogenital sinus, the so-called cloacal duct. At 15 mm. the cloaca is still not fully divided. At 15.5 mm. (approximately 7 weeks) the cloaca is just divided but the epithelium of the

12. Keibel and Mall,[11] p. 294.

13. Keibel and Mall,[11] pp. 314 and 322.

14. Keibel and Mall,[11] p. 834.

15. Keibel and Mall,[11] p. 871.

16. Bailey, F. R., and Miller, A. M.: Text-Book of Embryology, ed. 5. Baltimore, William Wood & Company, 1929, p. 370.

17. Keibel and Mall,[11] pp. 322 and 872.

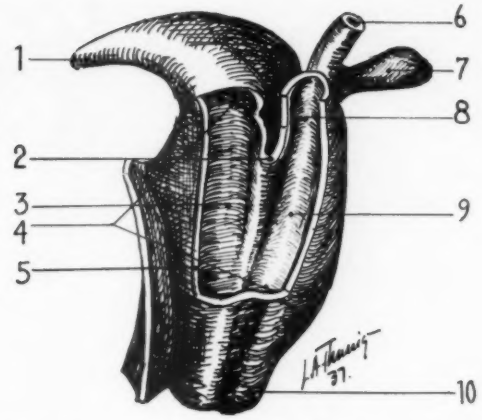

Fig. 7.—Model of the cloacal region in an embryo slightly older than that shown in figure 5: (modified copy of an illustration in Bailey and Miller [16] [p. 371]): *1*, urachus; *2*, urorectal fold; *3*, urogenital sinus; *4*, cloaca; *5*, cloacal membrane (laterally); *6*, mesonephric or wolffian duct; *7*, kidney or ureteral bud; *8*, intestine (hindgut); *9*, rectum, *10*, caudal gut.

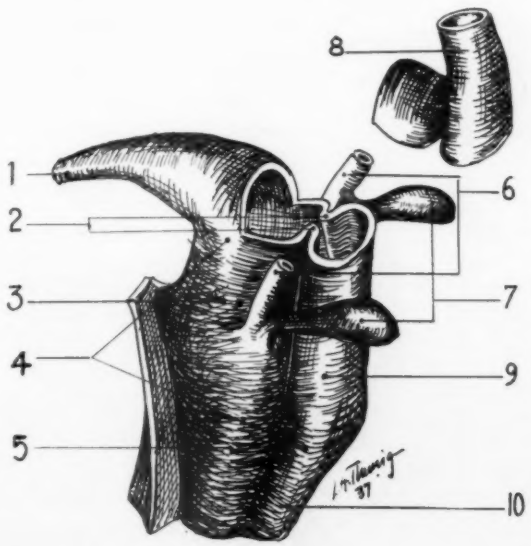

Fig. 8.—Reconstruction drawing of the cloaca, based on figure 7 and statements in the text and schematically sectioned to demonstrate the two lateral folds: *1*, urachus; *2*, urorectal folds; *3*, urogenital sinus (wall); *4*, cloaca (wall); *5*, cloacal membrane (laterally); *6*, mesonephric or wolffian ducts; *7*, kidney or ureteral buds; *8*, intestine (hindgut); *9*, rectum (wall); *10*, caudal gut.

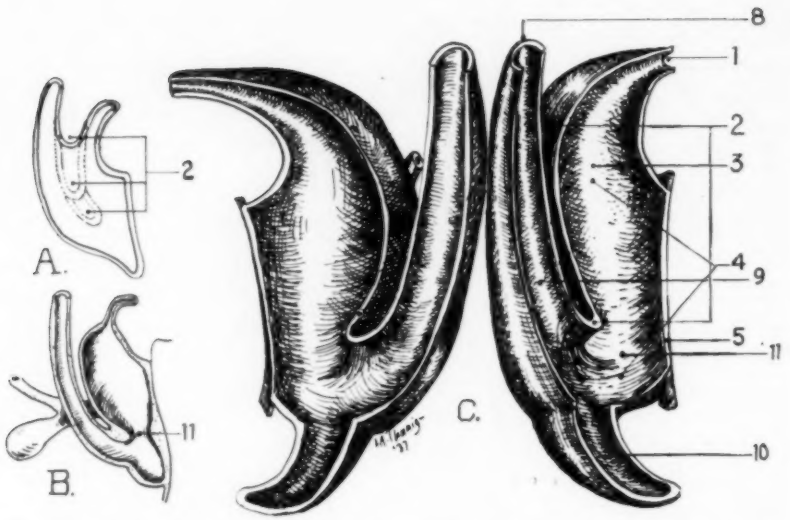

Fig. 9.—*A*, drawing of a model of the cloaca in a 7 mm. embryo in which the separation of the cloaca by an unpaired urorectal fold from above is shown diagrammatically (copied from an illustration in Keibel and Mall [11] [vol. 2, p. 872]). *B*, drawing of a model of a 7 mm. embryo, showing a sagittal section of the cloaca (copied from an illustration in Keibel and Mall [11] [vol. 2, p. 873]). *C*, schematic drawing (original) based on *A* and *B* and conforming for comparative reasons with figure 7 and figure 8. For purposes of demonstration the right half of the cloaca has been turned backward and is accordingly foreshortened. The parts are numbered as in figures 7 and 8: *1*, urachus; *2*, urorectal fold or (saddle); *3*, urogenital sinus; *4*, cloaca (undivided portion); *5*, cloacal membrane (ventrally); *6*, mesonephric ducts, hidden from view; *7*, kidney or ureteral buds, hidden; *8*, intestine (hindgut); *9*, rectum; *10*, caudal gut; *11*, cloacal duct of Reichel (1893).

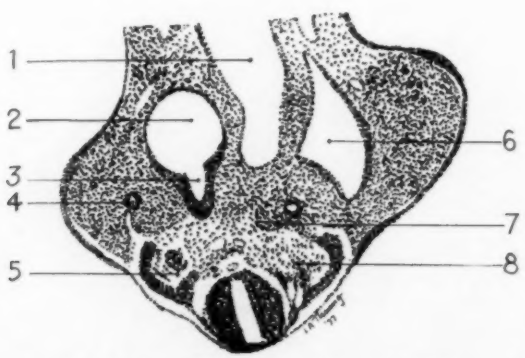

Fig. 10.—Drawing of a transverse section of a 4.7 mm. human embryo (copied from an illustration in Keibel and Mall [11] [vol. 2, p. 805]): *1*, left umbilical artery; *2*, urogenital portion of cloaca; *3*, rectal portion of cloaca; *4*, primary excretory mesonephric or wolffian duct; *5*, twenty-sixth primitive segment; *6*, coelum; *7*, metanephrogenic tissue; *8*, twenty-seventh primitive segment.

rectum and that of the urogenital sinus are still connected.[18] In other words, the cloacal membrane is still present. This leads to a discussion of the cloacal membrane. Before proceeding it may be well to recapitulate.

6. The allantois, mentioned in paragraph 4 as entering the cloaca, is now connected with the primitive bladder and the urogenital sinus by means of the urachus (originally the allantois). The ventral part of the cloaca (bladder and urogenital sinus) is now completely separated from the posterior part, the rectum down to the cloacal membrane.

7. The wolffian ducts and ureteral (or kidney) buds, last mentioned in paragraph 5, now show considerable advancement. The ureteral

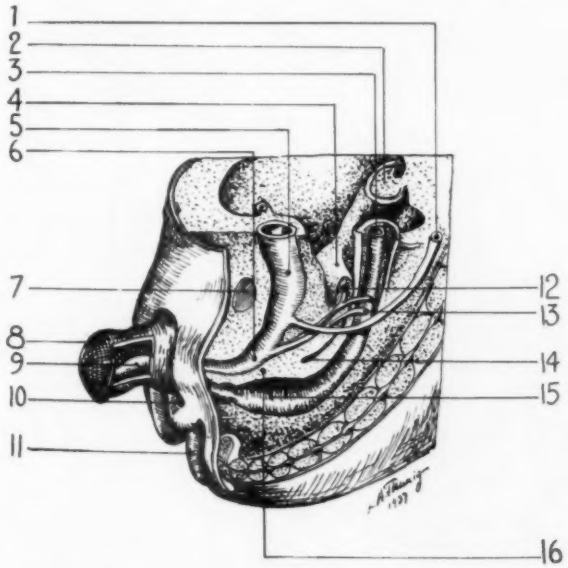

Fig. 11.—Reconstruction of the caudal end of a human embryo of 25 mm. (8½ to 9 weeks), one evidently destined to be a female, though the anatomic parts involved in the anomaly under discussion are still sexually undifferentiated (modified copy of an illustration in Bailey and Miller [16] [p. 372]): *1*, mesonephric or wolffian duct; *2*, genital gland or ovary; *3*, intestine; *4*, peritoneal fold (broad ligament); *5*, anlage for bladder; *6*, pars pelvina, urogenital sinus; *7*, symphysis; *8*, genital tubercle (phallus); *9*, pars phallica of urogenital sinus; *10*, anal membrane or anus; *11*, tail; *12*, müllerian duct; *13*, ureter; *14*, rectouterine excavation; *15*, rectum; *16*, urorectal fold.

[NOTE.—Embryologists refer to the primitive clitoris, as well as to the primitive penis, as the phallus.]

buds have grown backward, producing well defined ureters and renal pelves (fig. 6). At 10 to 14.5 mm. the terminal piece of the wolffian

18. Keibel and Mall,[11] p. 323.

duct on each side has been absorbed to form part of the bladder. The ureters and wolffian ducts open separately but close together in the vesicourethral portion of the urogenital sinus (fig. 11). The craniolateral migration of the ureters begins in the 13 mm. embryo. The wolffian ducts remain close together and at the same site at which they were; this site is to become Müller's hillock, which is to project into the urethra and form one of the points of the vesical trigon.[19] The

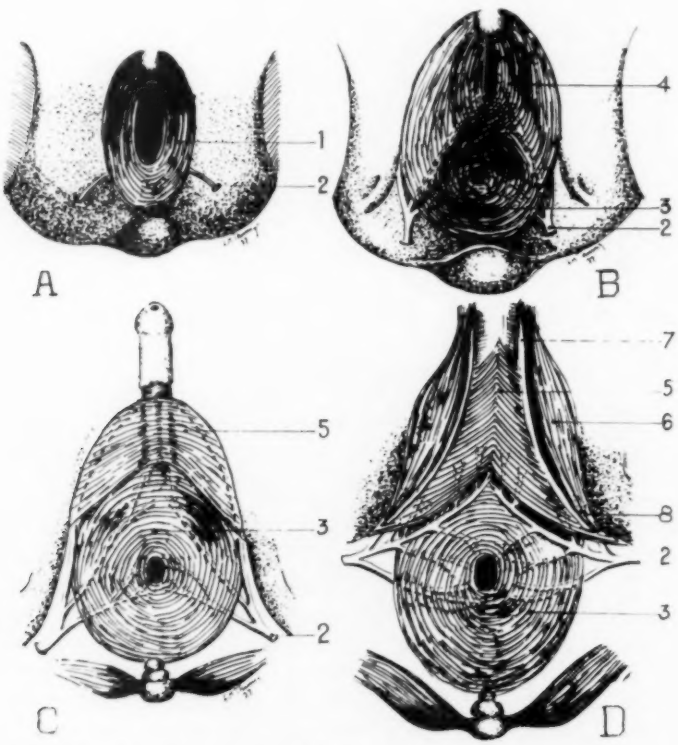

Fig. 12.—Muscles of the sexually indifferent and the male perineum. (These drawings were copied from an illustration in Keibel and Mall [11] [vol. 1, p. 479] reproduced from Popowsky, J.: Zur Entwickelungsgeschichte der Dammuskulatur beim Menschen, Anat. Hefte [Abt. 1], 1899, no. 38, p. 15, figs. 1, 2, 3 and 6). (*A*) an embryo of two months, (*B*) an embryo of three months, (*C*) a male fetus of four months and (*D*) a male fetus of five months: *1*, sphincter cloacae; *2*, pudendal nerve; *3*, sphincter ani externus; *4*, sphincter sinus urogenitalis; *5*, bulbocavernous muscle; *6*, ischiocavernous muscle; *7*, dorsal nerve of penis; *8*, nerve for ischiocavernous muscle.

caudal portions of the wolffian ducts become the vas deferens, and their ends in the urethra become the ejaculatory duct.[20]

19. Keibel and Mall,[11] pp. 877-878.
20. Bailey and Miller,[16] p. 386.

8. The rectum has now become independent and brings the hindgut down in direct continuity with that portion of the cloacal membrane now known as the anal membrane (figs. 11 and 15 *A*).

9. In order that the structure of the cloacal membrane (last mentioned in paragraph 5) may be understood, it is necessary to establish a few facts heretofore not mentioned in reference to the cloaca itself. The cloaca described in previous paragraphs is formed by entoderm, being derived directly from the hindgut. In addition to this entodermal cloaca, which, according to Keith, is the only part students of embryol-

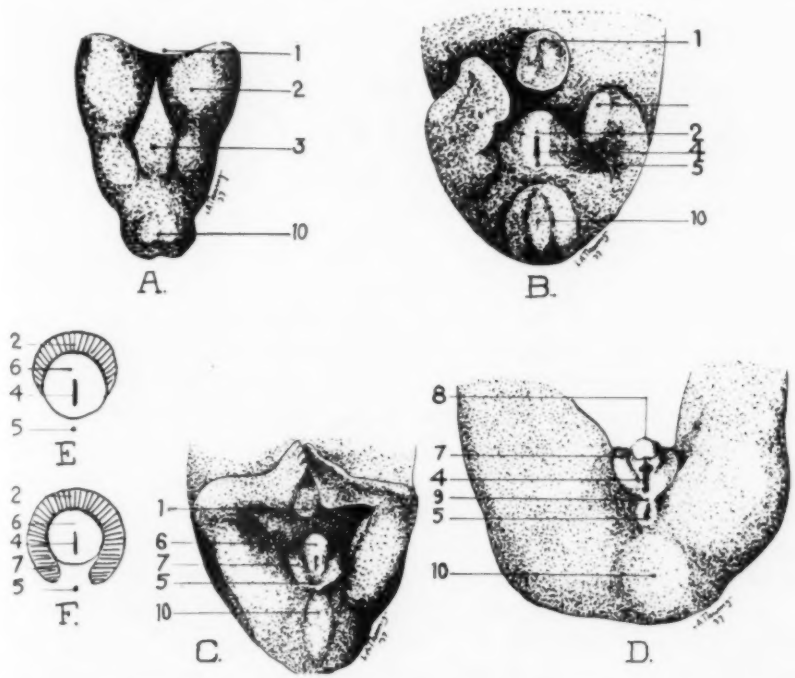

Fig. 13.—Development of external genitals in the male. *A*, model of the cloacal membrane of a human embryo of 3 mm. (copied from Keibel and Mall[11] [vol. 2, p. 872]). *B*, caudal end of a human embyro of 18 mm. *C*, indifferent external genitalia of an embryo of 28 mm. D, male external genitalia at 3½ months. (*B*, *C* and *D* are copied from photographs in Keibel and Mall [11] [vol. 2, pp. 947-950].) *E*, diagrammatic representation of the division of the cloacal tubercle into the phallus and the genital tubercle after Keibel and Mall [11] [vol. 2, p. 948]. *F*, diagrammatic representation of the formation of the genital swellings, based on figure 13 *E* and on text of Keibel and Mall.[11] Key to *A-F*: *1*, umbilicus; *2*, cloacal tubercle (paired in *A*); *3*, cloacal membrane; *4*, urogenital opening (present but not labeled in *C*); *5*, anal groove (*B*) anus (*C* and *D*); *6*, phallus; *7*, genital swelling (*C*); *8*, glans penis; *9*, unpaired scrotal area (see text); *10*, coccygeal tubercle.

ogy have in mind when they speak of the cloaca, there is a corresponding depression or sagittal groove (fig. 13) which is formed by ectoderm

and is known as the ectodermal cloaca.[21] In the human embryo of 11 to 13 mm. there is an oval pit (ectodermal cloaca) extending from the coccygeal prominence to the tip of the genital eminence.[22] Unquestionably there is some misconception in the general conception of the cloaca, and I believe this is due to the fact that one is accustomed to consider the human embryologic cloaca in terms of the cloaca of oviparous mammals or of birds. That is, one looks on the embryonal cloaca as an opening rather than as a closed sac. With that conception in mind it is difficult to visualize a cloacal membrane. But if one bears in mind [23] that the entodermal cloaca is a closed sac which is never normally opened outside (into the amniotic cavity [22]) and that its entodermal wall comes into contact with and fuses with the ectodermal wall of the ectodermal cloaca, or groove, the formation of the cloacal membrane is easy to comprehend (figs. 5, 6, 13 *A* and 16 *A*). Some embryologists have stated that the cloacal membrane consists of entoderm and ectoderm only, the mesoderm being pressed aside; others have stated that there is also a thin layer of mesoderm.[24]

10. The cloacal membrane is now intact (paragraphs 6 and 8) with the urorectal fold down to it. The cloacal membrane now consists of a urogenital membrane and a rectal membrane (figs. 15 *A* and 16 *A*). By referring to figure 13 *A* one notes that there are two cloacal tubercles (ectodermal) with the cloacal membrane between them forming a partition between the cavity of the entodermal cloaca and the groove of the ectodermal cloaca. In figure 13 *B* the cloacal tubercles have fused to form a single cloacal tubercle, and on the anal slope one sees the ectodermal cloaca with the urogenital opening and the anal groove. In figure 13 *C* the phallus is present, which develops and is seated on the cloacal tubercle like a tower on a hill.[25] At 22.8 mm. the area which was originally urorectal fold [18] shows mesodermal growth, with the development of a well marked primitive perineum; this is shown as the area between the anal area and the urogenital area in figures 11, 13 *B*, 13 *C* and 16 *A*. This primitive perineum is found at the bottom of the ectodermal cloaca. The anal membrane is also found in a depression at the bottom of the ectodermal cloaca; this depression is termed the anal pit or proctodeum (figs. 11, 13 *B* and 16 *A*). While these external changes have been taking place, internal changes have been keeping pace with them, particularly in the urogenital sinus. The points at which the ureters and wolffian ducts open mark the boundary between a slightly larger cephalic part of the urogenital sinus, the anlage

21. Keith,[10] p. 431. Keibel and Mall.[18]
22. Pohlman, A. G.: J. Anat. **12**:5, 1911.
23. Keibel and Mall,[11] p. 870.
24. Keibel and Mall.[23] Bailey and Miller.[16]
25. Keibel and Mall,[11] p. 948.

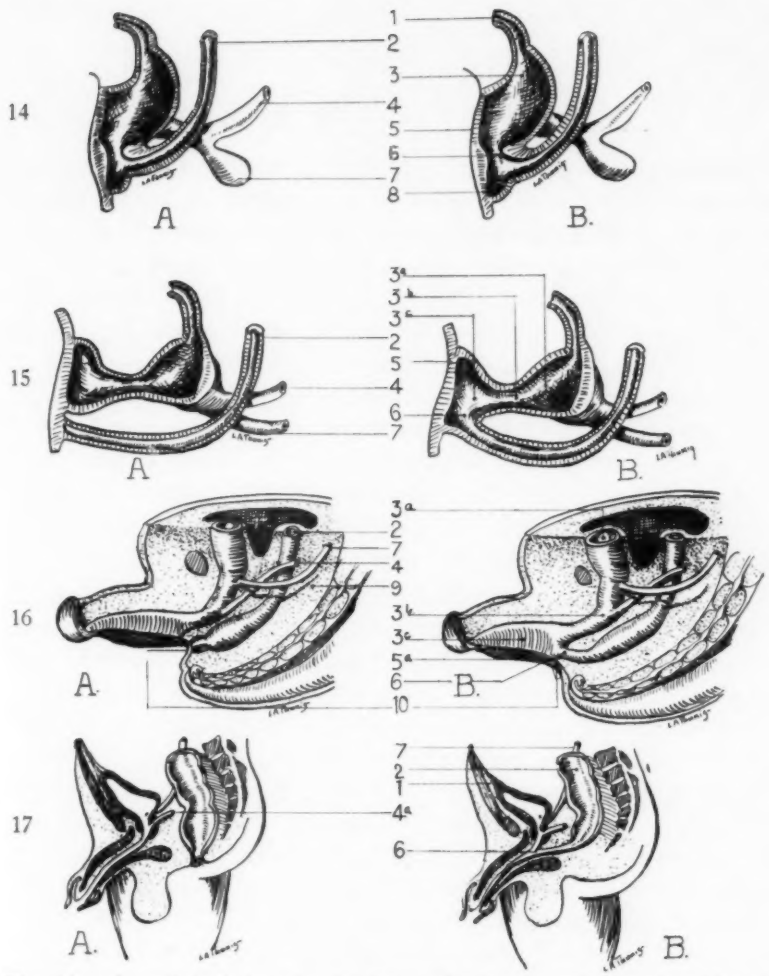

Fig. 14.—*A*, model of the normal cloaca of a 7 mm. embryo after Keibel and Mall [11] [vol. 2, p. 873]. *B*, model of the cloaca of a 7 mm. embryo. The text will show that up to this point the cloacal development in the anomaly was the same as in the normal.

Fig. 15.—*A*, model of the normal cloacal region of an 11 mm. embryo (copied from Keibel and Mall [11] [vol. 2, p. 874]). The rectum is completely separated from the urogenital sinus, which now shows three definite divisions. The caudal gut has disappeared. *B*, schematic drawing (original) of the anomalous clocaca. The urorectal fold has failed to separate the rectum from the urogenital sinus, and the cloacal duct persists.

Fig. 16.—*A*, drawing based on figure 11 and a drawing in Arey [39] [p. 146]. It is a reconstruction of the normal caudal end of a 25 mm. embryo. *B*, drawing showing the anomalous condition in development. The drawing is semidiagrammatic. The anal pit (proctodeum) and the entodermal anal membrane are missing. The persistent cloacal duct is now drawn out into a tract (see text).

Fig. 17.—*A*, semidiagrammatic representation of structures shown in figures 14 *A*, 15 *A* and 16 *A* as they appear at birth under normal conditions. *B*, semidiagrammatic representation of structures shown in figures 14 *B*, 15 *B* and 16 *B* as they were in the anomaly at birth. (See figs. 14, 15, 16 and 17). Key to *A* and *B*: *1*, urachus; *2*, rectum; *3*, urogenital sinus; *3a*, urogenital sinus—vesicourethral anlage; *3b*, urogenital sinus—pars pelvina; *3c*, urogenital sinus—pars phallica; *4*, mesonephric or wolffian or primary excretory duct; *4a*, mesonephric duct, now ejaculatory duct and terminal end of vas deferens and tubules of epididymis; *5*, cloacal membrane; *5a*, urogenital membrane (cloacal membrane); *6*, cloacal duct; *7*, ureteral or kidney bud and ureter; *8*, caudal gut; *9*, mesentery of rectum; *10*, anal pit (*A*) and anal site (*B*).

(primordium, literally "beginning") of the bladder and a small caudal part [26] which becomes the urethra and urogenital sinus (figs. 11, 16 *A* and 17 *A*). After the bladder begins to enlarge, the adjacent part of the urogenital sinus becomes slightly constricted (figs. 6, 11, 15 *A* and 16 *A*). This marks the proximal end of the male urethra.[26] Keibel and Mall [27] described the cloacal remains as becoming divided into a wide dorsal portion and a ventral portion with a narrow middle portion (figs. 6, 11 and 15 A). From the posterior broad lumen the vesicourethral anlage is formed; the narrow part becomes the pars pelvina of the urogenital sinus and the broad ventral part the pars phallica of the sinus urogenitalis.[27] The pars pelvina is the actively growing part which pushes the pars phallica before it.[28] Some believe that as the phallus grows the urogenital sinus (pars phallica) is drawn out into it.[29]

11. The urogenital membrane [30] runs along the anal slope of the cloacal tubercle and later along the phallus, in which organ it becomes enclosed (figs. 11 and 16 *A*). The breaking through of the urogenital membrane and anal membrane takes place independently, forming the anal orifice and urogenital orifice.[31] Keibel and Mall stated that the breaking through takes place in embryos between 13 and 18 mm., the anal opening being formed somewhat later than the urogenital.[31] They also stated: [32] "The perforation of the anal membrane normally takes place in embryos of 30 mm." Also: "In the Harvard collection there are embryos measuring 22 mm., 22.8 mm., and 29 mm. in which perforation has occurred, and specimens of 22.8 mm. and 30 mm., in which the anus seems still impervious." Also: "Keibel and Elze's series of 7 embryos measuring 22 to 26 mm., includes only 1 (22.5 mm.) in which the anus is open." From these statements one must conclude that the anal perforation takes place considerably later than the urogenital perforation if one accepts 13 to 18 mm. as being correct for the perforation of the urogenital membrane. The urogenital membrane ruptures normally when the division of the cloaca is complete.[22]

12. The foregoing paragraphs have presented a description of the development of the anus and rectum apart from its mesentery, the musculature controlling the same and the pushing backward of the anus which is due to an enlargement of the urorectal fold [33] (primitive perineum, paragraph 10). To refer again to figure 13 *C*: The formation of

26. Bailey and Miller,[16] p. 371.
27. Keibel and Mall,[11] p. 876.
28. Keibel and Mall,[11] pp. 962-963.
29. Johnson, F. P.: J. Urol. **4**:449, 1920.
30. Keibel and Mall.[27] Johnson.[29]
31. Keibel and Mall,[11] p. 872.
32. Keibel and Mall,[12] p. 324.
33. Bailey and Miller,[16] p. 394.

a phallus, referred to in paragraph 10, has divided the cloacal tubercle into a phallus and genital tubercle, as is shown diagrammatically in figure 13 *E*. The lateral growth of the genital tubercle as shown diagrammatically in figure 13 *F* has given rise to genital swellings as shown in figure 13 *C*. In figure 13 *D* the phallus has grown larger, and the glans penis is present. The glans is marked off in a 26 mm. embryo, and at three months the male phallus remains perpendicular to the body, and the female phallus bends downward.[34] Figure 13 *D* also shows the anus completed, with the urogenital sinus still open along the entire length of the phallus except the glans. That part of the urogenital sinus which is to form the glans portion of the urethra becomes perfectly solid and forms the urethral plate.[34] The urethral plate is eventually converted into the urethral groove and then closed over to form a tube [35] which becomes continuous with the phallic sinus urogenitalis, which by this time has also closed over, thus completing the entire penile portion of the urethra.[36] The prepuce is formed by an epithelial cylinder that grows in from the epithelium of the external surface of the glans penis.[36] In figure 13 *D* the genital swellings are seen to have become the scrotal swellings; the scrotum, however, with the descent of the testicles, is formed from that part designated in figure 13 *D* as the unpaired scrotal area into which the scrotal swellings extend. The scrotal swellings fade out into the surrounding areas.[37] According to Bailey and Miller [38] and Arey,[39] the scrotum is formed by fusion of the genital swellings, which fusion results in a raphe. When the raphe in the perineal region formed by the fusion of the ectodermal cloaca is present the permanent perineum is formed.[18] This raphe extends from the frenum of the prepuce to the anterior margin of the anus.[40]

13. With the exception of the muscles and the mesentery of the rectum the development of all embryonic structures closely related to the anomaly have been completed. I should like to add that the urachus finally becomes the middle umbilical ligament (fig. 17 *A*) and that the allantois, from which the urachus is derived, plays little part in the formation of the bladder, the bladder being formed almost wholly from the anterior part of the cloaca and from the inclusion of the bases of the wolffian ducts. If any part of the bladder is derived from the allantois, it is only the apex.[20]

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34. Keibel and Mall,[11] p. 949.
35. Keibel and Mall,[11] p. 964.
36. Keibel and Mall,[11] p. 955.
37. Keibel and Mall,[11] pp. 952-953.
38. Bailey and Miller,[16] p. 396.
39. Arey, L. B.: Developmental Anatomy, ed. 3, Philadelphia, W. B. Saunders Company, 1934, p. 164.
40. Keith,[10] p. 441.

14. The development of the muscles of the perineum can best be understood by referring to figure 12 and by quoting Keibel and Mall:[41]

> Popowsky has given the best account of the development of the muscles of the perineum. They arise from the musculus sphincter cloacae, a skin muscle, which is present in the 2 months embryo [fig. 12*A*]. During the third month of fetal life it divides into an M. sphincter ani externus and an M. sphincter sinus urogenitalis [fig. 12*B*]. This division is dependent upon the separation of the single cloacal opening into two openings. The M. sphincter ani externus alters very little during the later development, but the M. sphincter sinus urogenitalis undergoes many changes, giving rise as it does to perineal muscles. During the fourth and fifth months the M. sphincter urogenitalis gives rise first to M. ischiocavernosus, M. bulbocavernosus and M. sphincter urethrae membranaceae. The M. transversus perinei are the last ones to develop out of the peripheral and lateral part of the M. bulbocavernosus. The M. levator ani arises from quite a different source and only secondarily comes into relation with the M. sphincter ani and the perineal muscles. The M. levator ani arises in connection with the M. coccygeus and gradually descends to the rectum, bladder, prostate and vagina and thus comes into contact and intimate union with the muscles of this region. The difference in the nerve supply between the perineal muscles and the M. levator ani indicates their different origin.

This conception is followed by Keith.[40] Jordan and Kindred, cited by Young,[42] and Arey[43] maintained that the cloacal sphincter muscle is derived from the third and fourth coccygeal myotomes. Young stated that Otis (1905) found that the development of the external sphincter ani produces characteristic elevations. In embryos of 21 to 23 mm. there is a pair of external elevations, one on either side of the anal pit. At 26 mm. these unite to make the posterior side of the anus, forming a crescentic mound (fig. 13*C*). Finally the elevations meet anteriorly, encircling the anus.[44]

15. Regarding the internal sphincter ani, it has been stated that just before the rectum reaches the anal membrane it forms a bulbous enlargement (figs. 11 and 16*A*). In embryos of 17.5 mm. and 18.5 mm. the circular and longitudinal muscle fibers are easily recognized. The terminal swelling of the rectum extends beyond the muscle layers (Keibel, 1896). Keibel and Mall[32] described the musculature in a 29 mm. embryo as follows:

> The circular muscle layer ends very abruptly at the level of the little caudal swelling of the intestine, and already it may be referred to as the beginning of the muscle sphincter ani internus. The outer longitudinal layer of the intestinal musculature is arranged differently. It ends at the same level, but no sharp caudal limit can be recognized. The M. sphincter ani externus is clearly indicated and is relatively quite large. The cranial border of this muscle is found

41. Keibel and Mall,[11] pp. 478-480.
42. Young,[2] p. 576.
43. Arey,[39] p. 227.
44. Young,[2] p. 579. Keibel and Mall.[32]

where the musculature of the intestine ends, therefore at the level of the little caudal entodermal enlargement. The M. sphincter ani externus is separated from the epithelium of the intestine by a rather thin layer of connective tissue, which is continuous with the connective tissue surrounding the intestine further cranially, and also with the longitudinal layer of the muscularis, from which strands of cells may be followed into it.

16. In my opinion the peritoneum is also a factor in the anomaly under discussion, not as a causative factor but as an important modifier of the anatomic relations of the structures involved in the anomaly. Almost as soon as the mesoderm is formed it splits into two parts. The space between these two parts becomes the coelum and the inner layer joins with the entoderm and forms the primitive mesenteries. The lower part of the gastrointestinal tract, or hindgut, has only a posterior mesentery.[45]

Previous to the middle of the fourth month, the gut is freely movable within the scope of its restraining mesentery but soon secondary adhesions occur which attach certain segments. The ascending colon and descending colon are applied against the body wall on the right and left sides respectively.[46]

Keith[47] stated: "The adhesions as they form, contract and thus draw the various parts of the alimentary canal to their final position."

17. Summary: The description of the development of all embryonic structures related closely to the anomaly under discussion has been carried forward to the completion of the process or to a developmental stage beyond which there could be no further possible relation with this specific anomaly either in the positive sense of being a factor directly productive of error or in the negative sense of limiting the error to the factor suspected of producing it.

CORRELATION OF EMBRYOLOGIC FACTS WITH ANATOMIC AND CLINICAL FINDINGS

[NOTE.—It is assumed here that structures and organs which were not found abnormal at operation and which did not at the time of birth or during the successive eleven years show themselves to be abnormal either anatomically or functionally are, in all probability, normal.]

The following structures and organs, closely related embryologically, were normal at birth and during the following eleven years:

1. Umbilicus and attachment of the umbilical cord.
2. Penis and penile portion of the urethra (pars cavernosa) to the point of junction of the urethrorectal fistula.
3. Testes and scrotum.
4. Bladder, membranous portion of the urethra, prostatic portion of the urethra, ureters and pelves of the kidneys.

45. Keith,[10] p. 303. Bailey and Miller,[16] p. 347.
46. Arey,[39] p. 125.
47. Keith,[10] p. 326.

5. Sphincter urethrae membranaceae and vesical musculature, including vesical sphincter (annulus urethralis).

The following structures were abnormal:

1. Anus.
2. Sphincter ani externus.
3. Lower part of the rectum.
4. Sphincter ani internus.
5. Fistula or tract between the rectum and the urethra.

From these facts, in view of the embryologic study, one may with reasonable certainty assume:

1. The allantois went to its normal termination as the middle umbilical ligament. (See section on embryology, paragraphs 4, 6 and 13, and figs. 3, 4, 5, 6, 7, 8, 9, 14, 15 and 17.)

2. Normal development took place in the fusion of the cloacal tubercles into one and the subsequent development of the penis was normal. Also, the pars pelvina and pars phallica of the urogenital sinus and urethral plate went on to the normal development of the prostatic, membranous and cavernous (penile) portions of the urethra up to the point of the beginning of the tract between the penile portion of the urethra and the rectum. (See section on embryology, paragraphs 10, 11 and 12, and figs. 1, 2, 11, 13, 16 and 17.)

3. The testes apparently developed normally and descended normally into a scrotum which developed normally from the genital folds or the unpaired scrotal area. (See section on embryology, paragraphs 7 and 12, and figs. 1, 2, 13 *C*, 13 *D* and 17. In these illustrations the testes have been omitted to prevent confusion.)

4. The bladder anlage portion of the urogenital sinus went forward to the development of a normal bladder. Likewise, the ureteral or kidney buds formed normal ureters and renal pelves. The fact that the lower part of the bladder was apparently normal leads one to believe that the wolffian ducts, from the lower ends of which the mesodermal portion of the bladder is formed,[48] developed normally. (See section on embryology, paragraphs 5, 7, 10 and 13, and figs. 1, 2, 5, 6, 7, 8, 9, 11, 16 and 17.)

5. The normal emptying and the normal sphincteric action and control of the bladder at birth and for eleven years afterward indicate that the original sphincter cloacae developed normally to form the sphincter urethrae membranaceae and that the musculature of the bladder with the formation of the annulus urethralis (vesical sphincter) took place in the normal manner. (See section on embryology, paragraph 14, and fig. 12.)

48. Keibel and Mall,[11] p. 878.

6. The anus was completely absent at birth. One of two conditions may have been present during embryologic growth:

(*a*) The proctodeum, or anal pit, of the ectodermal cloaca may never have formed.

(*b*) It may have formed, but owing to the abnormal behavior of the entodermal cloaca and urorectal fold, as will be shown in a later paragraph, no entodermal anal membrane was present, and the existing anal pit of the ectoderm may have been filled out by connective tissue from above and thus obliterated. Keibel and Mall [49] commented on this connective tissue infiltration. The fact that every other part of the ectodermal cloaca (the phallus, genital folds and urogenital sinus membrane) developed normally leads me to believe that at some time the anal pit had been present. (See section on embryology, paragraphs 5, 8, 9, 10, 11, 12 and 14, and figs. 1, 2, 5, 6, 7, 8, 9, 11, 13, 14, 15, 16 and 17.)

7. At birth, as has been stated, there was no indication of an anus, nor did I see or feel the elevations caused by the presence of an external sphincter ani as described in paragraph 14 of the section on embryology and mentioned by Young [50] in a case in which a dimple was present at the anal site and the sphincter could be felt and made to contract with a pin prick. It is possible that had I palpated the anal area more carefully or been informed of the pin prick test I might have determined the presence of the sphincter. That a sphincter was present is without question, as was demonstrated by the functionally good anus which resulted after operation. The presence of a sphincter ani further establishes the fact that the cloacal sphincter developed normally. That others, like myself, have been unable to find any trace of an anus is corroborated by at least one excellent observer.[51] (See section on embryology, paragraphs 9, 10, 11 and 14, and figs. 1, 2, 12, 13, 16 and 17.)

8. The presence of the rectal pouch, as found at operation, in the curve of the sacrum and close to the sacrum indicated that some fixation of the posterior rectal mesentery had taken place. (See section on embryology paragraph 16, and figs. 1, 2, 16 and 17.)

9. Regarding the internal sphincter ani, it can be definitely stated that at operation no caudal thickening or swelling of the rectum was seen or felt. The part of the rectum at which this swelling should normally be present was involved in the main part of the anomaly, to be described in the next paragraph. One cannot definitely state that the internal sphincter was absent, but one can state that it was not normal

49. Keibel and Mall,[11] p. 325.

50. Young,[2] pp. 556-557.

51. Wakeley, C. P. C.: J. Anat. **57**:216, 1923.

in size or location. (See section on embryology, paragraph 15, and figs. 11 and 15 *A*).

10. The presence of the tract or fistula between the rectal pouch and the posterior part of the penile portion of the urethra in this case was apparently due to two factors:

(*a*) The determining factor of the entire anomaly, which was the abnormal behavior of the urorectal fold in not completing its descent to the cloacal membrane. This resulted in two definite errors: The first was a persistent opening between the rectum and the pars phallica of the urogenital sinus, the opening having the diameter of the rectum; in other words, there was a persistent cloacal duct, as shown in figure 15 *B*. The second error was a failure of localization of an entodermal anal membrane.

(*b*) The modifying factors, which converted the large persistent cloacal duct into a comparatively narrow tract of some length, as found at operation, between the rectal pouch and the penile portion of the urethra. I believe that a very small part of this tract consisted of a part of the posterior or proximal part of the penile portion of the urethra, and the major part, of the terminal portion of the rectum, including that part of the rectum which normally should form the internal sphincter, and that the factors producing this result were the gradual pulling back of the rectum into the sacral curve, as found at operation, by a continued effort at fixation of the lower part of the rectum by its mesentery, and by the downgrowth of mesodermal connective tissue around the tract, this connective tissue normally forming the perineum and causing a normal posterior displacement of the lower part of the rectum and of the anus. The normal pushing forward of the pars phallica by the pars pelvina of the urogenital sinus may also have been contributory in converting the opening into a tract. The fact that the lower part of the rectum was at least 1½ to 2 inches (3.7 to 5 cm.) above the perineal level and the fact that the abnormal tract was also some distance from the perineum make it seem probable that there was also a growth of connective tissue from below, possibly from the mesoderm, which by some authors is said to exist in the cloacal membrane and by others to be pushed to the side of the cloacal membrane. At operation connective tissue was present in the areas just described. In paragraph 6 of this section on correlation the absence of the anus was discussed. In view of what has just been stated, a comparison of figures 16 *A* and 16 *B* discloses that even if a definite proctodeum had formed (as in figure 16 *A*) there would have been no rectum with which it could have united to form a normal anal orifice; this is demonstrated in figure 16 *B*. (See section on embryology, paragraphs 5, 6, 8, 9, 10, 11, 12 and 16, and figs. 1, 2, 6, 7, 8, 9, 14, 15, 16 and 17.)

Time at Which the Anomaly Was Determined.—It must be borne in mind that there is considerable variation in the relation of size to the stage of development of many of the structures mentioned in this article. This is unquestionably due to the fact that variation occurs in different embryos. For example, Keibel and Mall [18] stated that in Keibel and Elze's cases, a cloacal duct was present in 11 and 12.5 mm. embryos, that at 15 mm. the cloaca was not fully divided and that it was divided down to the cloacal membrane only at 15.5 mm.; yet they presented a drawing,[52] a copy of which is shown in figure 15, of a model of an embryo of only 11 mm. in which the cloaca is divided down to the cloacal membrane. Allowing for these minor variations, one may say:

1. At five weeks the cloaca is undivided. (See section on embryology, paragraphs 3 and 5, and fig. 5.)

2. At 6 weeks the cloaca is divided almost to the cloacal membrane, with the formation of a cloacal duct. (See section on embryology, paragraphs 3 and 5, and figs. 6, 9 *B* and 14.)

3. At 7 weeks the cloaca is completely divided down to the cloacal membrane. (See section on embryology, paragraphs 3 and 5, and fig. 15 *A*.)

4. At a little less than 8 to 9 weeks the primitive perineum is evident, and the anal pit is also present. (See section on embryology, paragraphs 3 and 10, and figs. 11, 13 *B* and 16 *A*.)

5. From the eighth to the ninth week the anal membrane breaks through to form the anal canal. (See section on embryology, paragraphs 3 and 11, and fig. 13 *C*.)

6. After the middle of the fourth month mesenteric fixation takes place and is continued until birth. (See section on embryology, paragraph 16.)

7. From these statements one may conclude with reasonable certainty that the anomaly started at about the sixth week and was definitely determined at the seventh week so far as the connections between the rectum and the pars phallica of the urogenital sinus is concerned. At from eight to nine weeks the absence of the anus was determined. The changing of a simple opening between the rectum and the penile portion of the urethra (pars phallica) into a definite tract was a secondary and later development which started at about eight to nine weeks with the laying down of the primitive perineum by mesodermal connective tissue and which was augmented after four and one-half months by the continual effort at fixation of the lower part of the rectum by the posterior mesentery until birth. The pushing forward of the pars phal-

52. Keibel and Mall,[11] p. 874.

lica of the urogenital sinus by the pars pelvina begins with the development of the phallus at eight and a half to nine weeks.

Summary.—Two definite but closely related and dependent anomalies existed: (1) an abnormal lower rectal part which had been stretched out into a tract of small caliber to communicate with the proximal part of the penile portion of the urethra and (2) a complete absence of the anal canal, with an imperforate external sphincter.

The first of these was caused primarily by a persistent cloacal duct which the constant effort at fixation of the lower part of the rectum by its mesentery and invasion by connective tissue converted into a tract, largely at the expense of the terminal portion of the rectum and its internal sphincter. The second in all probability was dependent on the first. The anal pit was probably present at some time, but owing to the misbehavior of the entodermal cloaca no connection of the ectodermal and of the entodermal membrane and anal pit with the terminal portion of the rectum could be established; hence, the anal pit was completely obliterated and smoothed out by connective tissue. This, in view of the facts presented, seems far more likely than that no anal pit was formed.

The anomaly was caused entirely by the factors just stated. The embryonic development of all other structures intimately related had no direct or contributory influence on the development of the anomaly.

The anomaly was determined at about the sixth week of embryonic life and was modified throughout the remainder of intrauterine life until it reached the development present at the time of birth.

SUMMARY AND CONCLUSIONS

A rare anomaly is presented. The patient, a boy, was operated on at 48 hours of age by primary perineal plastic operation. An attempt was made to establish an anus and to close the fistula between the urethra and the rectum.

The result of the operation was a very good anus with effective, if not absolutely perfect, sphincteric control for the period of eleven years during which the patient was under observation. The eradication of the connection between the rectum and the urethra was accomplished, but a fistula between the urethra and the perineal-anal junction, which leaked urine in small amounts during urination only, remained. The major portion of the urine was simultaneously passed in a normal manner through the penile urethra.

Operation for the remaining urethroperineal fistula was postponed until the boy should be older, in better health and more manageable.

The embryologic development of this anomaly can, in my opinion, be clearly explained, as can the approximate time of its determination.

I admit that in attempting to explain an anomaly of this type a certain amount of conjecture is bound to enter, but I am convinced that just as normal embryology included in the beginning much conjecture, which was gradually replaced by facts through minute examination of many normal human embryos, just so careful operative or postmortem examination of every available anomaly will eventually, with compilation of the various findings and correlation of these with normal embryology, replace conjecture with well established facts.

Thus convinced, I have undertaken to correlate normal embryology with the anatomy, function and clinical aspects of one specific anomaly, trying always to confine may statements to authentic facts and drawing, I trust, logical conclusions therefrom. If conjecture or faulty deductions have entered the analysis, they may prove a stimulus to others to express their views and bring these fallacies to light.

ETHYL ALCOHOL AS A GERMICIDE

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Alcohol is probably the most popular of all cutaneous disinfectants. It is generally used in every country, not only in dressing wounds and in preoperative preparation of the surgeon's hands and the field of operation, but for a multitude of minor procedures, such as vaccinations, hypodermic injections and punctures of the skin for blood counts. Reasons for its popularity are obvious: It is relatively cheap and easy to obtain, it is pleasant to use and it "wets" the skin efficiently. An alcohol-soaked pledget can wipe away a certain amount of grease and dirt, and in universal experience its application seems capable of preventing infections from needle punctures and the like.

Laboratory tests, however, as reported in the literature, have on the whole shown alcohol to be but weakly bactericidal, and the prevailing conclusion of present day writers is that whatever efficiency it may have as a cutaneous disinfectant is due mainly to detergent properties.

A study of disinfectants, carried on over a period of several years, has led me to a different point of view. Using original quantitative tests of bactericidal activity, I have found ethyl alcohol, within certain narrow limits of concentration, to be strongly germicidal, both in vitro and on the skin. In addition, certain principles have been discovered which, I believe, govern the proper preparation and effective use of alcohol in surgical procedures.

HISTORICAL REVIEW

Alcohol in wine or in other impure forms has been used for local application in surgical practice since time immemorial. The present connotation of the term, however, is modern.

Lowitz [1] (1796) was the first to prepare alcohol containing less than 5 per cent of water.

Koch [2] (1881) in his monumental study of disinfectants found dilute alcohol a relatively weak bactericide and absolute alcohol as indifferent "as sterile water" against anthrax spores.

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1. Lowitz, in Thorpe, T. E.: A Dictionary of Applied Chemistry, London, Longmans, Green & Co., 1898-1900.

2. Koch, R.: Zur Untersuchung von pathogenen Organismen, Mitth. a. d. k. Gsndhtsamte **1**:1, 1881.

It is significant that the comprehensive report of the committee on disinfectants of the American Public Health Association [3] (1888) made no mention of alcohol. Furthermore, in this period of intensive study of bacteria and bactericides, many investigators, including Koch, used alcohol to wash bacteria free from the disinfectant under investigation, unconsciously attributing to the disinfectant any contributory bacteriotoxic or bactericidal action of the alcohol.

Fürbringer [4] (1888) recommended alcohol as an accessory in preoperative preparation of the hands, to remove fatty material from the skin and permit better contact between the cutaneous bacteria and the germicide to follow. He suggested a procedure (washing in water with brush and soap for one or more minutes, in 80 per cent [or stronger] alcohol for one minute and in 3 per cent phenol or 1 : 500 or 1 : 1,000 mercury bichloride solution for one minute) which he claimed was able as a rule to "sterilize" the hands. Modifications of this simple routine have outlasted all other methods of disinfection of the hands.

Reinicke [5] (1894) suggested that alcohol might have some disinfectant as well as cleansing action on the skin and advocated washing for three to five minutes in 90 per cent solution.

Krönig [6] (1894), unable to kill Staphylococcus aureus in vitro with 95 per cent alcohol, suggested that the apparent effectiveness of alcohol in surgical procedures might be due to dehydrating and astringent action, the bacteria being held in the shrunken skin.

Ahfeld [7] (1896) concluded that it is necessary for micro-organisms to be wet for alcohol to be most effective and that skin and mucous membranes are disinfected by a "diffusion-stream" of water and alcohol.

Epstein [8] (1897), in the most carefully conducted experiments up to that time, using various sorts of organisms dried on bits of silk thread, found that of the solutions tested (25, 40, 50, 80, 95 and 99 per cent) the most germicidal was the 50 per cent solution, which was capable of killing test bacteria in five to ten minutes. It is remarkable how many modern textbooks in discussing the disinfectant action of alcohol refer only to this work of Epstein.

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3. Disinfection and Disinfectants, Report of the Committee on Disinfectants of the American Public Health Association, Concord, N. J., Republican Press Association, 1888.

4. Fürbringer, P.: Untersuchungen und Vorschriften über die Desinfektion der Hände des Arztes, Wiesbaden, J. F. Bergmann, 1888.

5. Reinicke, E. A.: Bakteriologische Untersuchungen über die Desinfektion der Hände, Centralbl. f. Gynäk. **18**:1189, 1894; Arch. f. Gynäk. **49**:515, 1895.

6. Krönig, E. A.: Versuche über Spiritusdesinfektion der Hände, Centralbl. f. Gynäk. **18**:3, 1894.

7. Ahfeld, F.: Die Wirkung des Alkohols bei der geburtshülflichen Desinfektion, Deutsche med. Wchnschr. **6**:81, 1896.

8. Epstein, F.: Zur Frage der Alkoholdesinfection, Ztschr. f. Hyg. u. Infectionskr. **24**:1, 1897.

Minervini [9] (1898), Salzwedel and Elsner [10] (1900) and others corroborated Epstein's work in general but found that different bacteria show varying degrees of resistance to alcoholic action.

Harrington [11] (1903) demonstrated convincingly that micro-organisms are more susceptible to alcohol when moist than when dry on threads and garnets. He found 60 to 70 per cent the most effective strength against the common vegetative germs (when dry), killing them in five minutes or less at room temperature.

Beyer [12] (1911), in a careful study that has not received due recognition, pointed out the important difference between concentrations by volume and concentrations by weight and showed the great superiority of a solution of alcohol exactly 70 per cent by weight. He claimed that a 70 per cent solution is thirty times as powerful as a 60 per cent and forty times as powerful as an 80 per cent solution and that solutions less than 50 per cent or over 80 per cent (by weight) are of no practical value in disinfection. Failing in his efforts to use suspensions of bacteria because of the rapid bactericidal action of alcohol, he resorted in his experiments to use of Staph. aureus dried on silk threads (table 3 and chart 3).

Gregersen [13] (1915) and Christiansen [14] (1918) repeated Beyer's work with modifications and with slightly different results. They used Staph. aureus dried on garnets. Both investigators found somewhat wider ranges in strength of alcohol to be effective. Gregersen concluded that 70 per cent (by weight) is the concentration of maximum power; Christiansen, 80 per cent (table 3). Christiansen also pointed out a relation between low surface tension and disinfecting power.

Frey [15] (1912) attempted to explain Beyer's results on biochemical grounds, calling attention to the fact that the action of alcohol on albumins is maximal when its concentration is 70 per cent by weight.

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9. Minervini, R.: Ueber die bactericide Wirkung des Alkohols, Ztschr. f. Hyg. u. Infectionskr. **29**:117, 1898.

10. Salzwedel and Elsner: Ueber die Werthigkeit des Alkohols als Desinfectionsmittel und zur Theorie seiner Wirkung, Berl. klin. Wchnschr. **37**:496, 1900.

11. Harrington, C.: The Germicidal Action of Alcohol, Boston M. & S. J. **148**:548, 1903.

12. Beyer, A.: Alkoholdesinfektion, Ztschr. f. Hyg. u. Infektionskr. **70**:225, 1911.

13. Gregersen, J. P.: Untersuchungen über die desinfizierende Kraft der desinfizierenden Stoffe im Verhältnis zu ihrer Konzentration, Zentralbl. f. Bakt. (Abt. 1) **77**:168, 1916.

14. Christiansen, J.: Zur Theorie und Praxis der Alkoholdesinfektion, Ztschr. f. physiol. Chem. **102**:275, 1918.

15. Frey, E.: Warum wirkt gerade 70%iger Alkohol so stark bakterizid? Deutsche med. Wchnschr. **38**:1633, 1912.

Bills[16] (1926) in a study of fat solvents reported ethyl alcohol to be immiscible with cod liver oil, linseed oil, olive oil and butter and coconut fats. [This throws doubt on the usual teaching that alcohol acts chiefly as a detergent, dissolving the grease and oils on the skin.]

Gershenfeld[17] (1938) found that 95 per cent alcohol requires seven to nine months to kill spores of Bacillus megatherium and Bacillus subtilis and that 2 per cent alcohol in culture mediums is not even bacteriostatic for these organisms.

The foregoing review indicates a singular lack of agreement among outstanding investigators as regards the germicidal power of alcohol, its most potent concentrations and the nature of its action on skin—a lack of agreement reflected in surgical technic today. It was in the attempt to throw light on these problems that the studies reported here were undertaken.

EFFECT OF ALCOHOL ON BACTERIAL FLORA OF SKIN

A method (Price,[18] 1938) was used whereby the effect of a germicide on the bacterial flora of skin may be determined quantitatively. In each of these experiments the hands and arms were first scrubbed repeatedly with sterile water, the washings being used to determine the size of the flora on which the germicide was to act. The entire cutaneous area was then washed in the alcohol solution, care being taken in most instances to avoid friction of any sort. Exactly at the end of the test period all germicidal action was terminated by plunging the hands and arms into sterile water. Scrubbing was then resumed in a second series of basins in order to ascertain the number of viable organisms remaining on the hands and arms. From these determinations the effect of the alcohol could be deduced with a fair degree of precision. To illustrate more fully how such tests are carried out, details of one of them are given in table 1 and chart 1.

Summary results of several such experiments with different solutions of alcohol are shown in table 2.

It will be seen that the 60 per cent solution has almost the same degerming effect as scrubbing, whereas the solutions approximating 70 per cent (by weight) are considerably more efficacious. In solutions above 70 per cent the germicidal power decreases.

Moreover, a comparison of experiment 1 with experiment 2, and of experiment 4 with experiment 5 suggests that degermation of the

16. Bills, C. E.: Fat Solvents, J. Biol. Chem. **67**:279, 1926.

17. Gershenfeld, L.: The Sterility of Alcohol, Am. J. M. Sc. **195**:358, 1938.

18. Price, P. B.: The Bacteriology of Normal Skin: A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleansing, J. Infect. Dis. **63**:301. 1938.

TABLE 1.—*Quantitative Measurement of the Effect of 65.5 Per Cent Alcohol on the Bacterial Flora of the Hands and Arms*

Basin	Scrubbing Time, Minutes	Total Bacterial Count for Basin	Cumulative Totals Washed Off	Actual Totals, or Number of Organisms Left*
				7,922,090 (*a*)
1	1	1,640,450	5,222,090	6,281,640
2	1	841,750	3,581,640	5,439,890
3	2	1,211,910	2,739,890	4,227,980
4	1	436,800	1,527,980	3,791,180
5	1	348,840	1,091,180	3,442,340
6	1	403,760	742,340	3,038,580
7	1	338,580	338,580	2,700,000 (*b*)
At this point hands and arms were washed without friction in 65.5% (by weight) alcohol for exactly 60 seconds. Scrubbing was resumed immediately. The temperature of the alcohol was 25 C.				
				1,686,910 (*c*)
8	1	146,260	1,036,910	1,540,650
9	1	143,520	890,560	1,397,130
10	1	143,940	747,130	1,253,190
11	1	159,250	603,190	1,093,940
12	1	113,400	443,940	980,540
13	1	133,980	330,540	846,560
14	1.5	196,560	196,560	650,000 (*d*)

* Total number of bacteria on the hands and arms (*a*) at the beginning of the experiment; (*b*) after eight minutes of scrubbing; (*c*) after application of the germicide, and (*d*) after the second period of scrubbing. The numbers *b* and *d* are arrived at by mathematical projection of the curves produced (fig. 1).

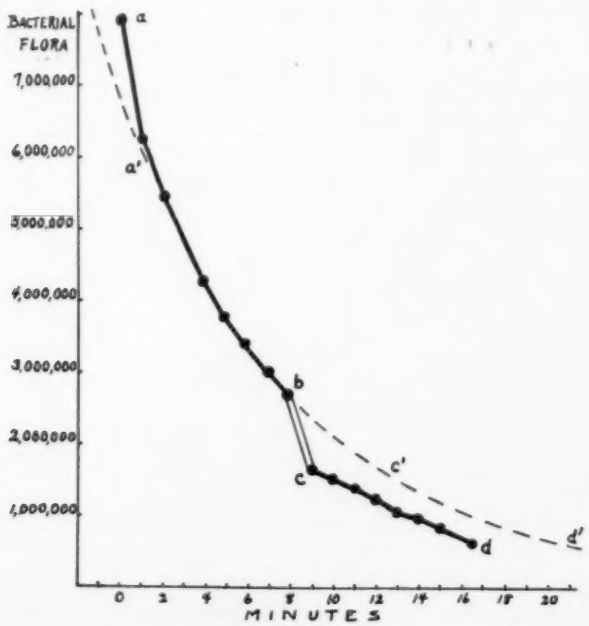

Chart 1.—Effect of 65.5 per cent alcohol on the bacterial flora of the hands and arms. The broken line *a'c'd'* represents the rate at which the basic flora of my own hands and arms are always degermed by scrubbing in a standard manner. The solid line *ab* indicates the effect of scrubbing eight minutes, while *cd* shows the result of scrubbing seven and one-half minutes in the second series of basins. The initial deviation *aa'* from the standard shows that there were about 1,000,000 contaminating or "foreign" bacteria on the skin, most of which were washed off in the first basin. The second deviation *bc* was due to use of the alcohol. Note that the same result would have been obtained if instead of washing in alcohol for one minute scrubbing had been prolonged for four and two-tenths minutes, from *b* to *c'*. *cd* is equivalent to *c'd'*. Hence each minute the hands are kept in this particular solution of alcohol may be said to be equivalent to four and two-tenths minutes of scrubbing.

skin by solutions of alcohol proceeds, as in scrubbing, at regularly logarithmic rates. Further studies have confirmed that observation. Consequently, it is possible accurately to express the effect of the chemical agent in terms of equivalent scrubbing time. Thus, washing for one minute in 69.5 per cent alcohol is equivalent to scrubbing for six and forty-seven hundredths minutes (experiment 5); therefore, washing in that solution for five minutes would have the same result as thirty-two and thirty-five hundredths minutes (5×6.47) of scrubbing. I have found this always to be true, irrespective of the size of the original flora.

In the first 6 experiments (in table 2) particular care was taken to avoid as far as possible any mechanical factor in the action of alcohol on bacteria of the skin. In previous experiments (reported elsewhere)

TABLE 2.—*Effect of Different Strengths of Alcohol on the Bacterial Flora of the Hands and Arms*

Experiment No.	Alcohol Solution Used, Wt. %	Temperature of Alcohol, C.	Length of Time Used, Min.	Friction	Total Organisms		Equivalent in Scrubbing Time	
					Before Use of Alcohol	After Use of Alcohol	Actual, Min.	Per Min. of Use, Min.
1	59.0	25.5	5	None	1,295,000	660,000	5.33	1.07
2	60.0	24.5	3	None	4,100,000	2,925,000	3.03	1.01
3	65.5	25.0	1	None	2,700,000	1,687,000	4.20	4.20
4	69.0	25.0	3	None	1,400,000	164,000	19.90	6.30
5	69.5	25.0	1	None	2,227,000	1,072,000	6.47	6.47
6	78.5	25.0	1	None	550,000	318,000	4.90	4.90
7	61.0	?	1	Brush	4,350,000	957,000	13.33	13.33
8	70.0	25.0	3	Gauze	1,060,000	29,000	33.74	11.25

it was found that scrubbing with a brush is much more effective in reducing the cutaneous flora than ordinary washing (rubbing the hands together) and many times as efficient as simple rinsing. It seemed probable, therefore, that the action of alcohol would be enhanced by brushing or rubbing the skin. In fact, some heroic surgeons of the past generation advocated and practiced brushing with alcohol, and today many operators are accustomed to rub their hands and arms with gauze soaked in alcohol, but probably more with the idea of cleansing the skin than with any thought of increasing the germicidal effect of alcohol.

Chart 2 shows graphically the result of brushing the skin with 61 per cent alcohol. This relatively inactive concentration was chosen to avoid totals so small, for the second series of basins, as to be hard to plot accurately. A brush ordinarily used for scrubbing was employed. The brushing caused smarting, especially of the arms, sufficiently severe to suggest why the method has never come into general use. Comparison of experiments 2 and 7 shows clearly that brushing has increased enormously the bactericidal effect of alcohol.

Tests have also been made of the effect of rubbing the skin with gauze and 70 per cent (by weight) alcohol. Results of 1 such experiment are shown in table 2 (experiment 8). Before entering the germicide the skin was permitted to dry to avoid any change in concentration of the alcohol by water carried on the hands. Comparison with experiments 4 and 5 indicates that friction in this case almost doubled the bactericidal effect.

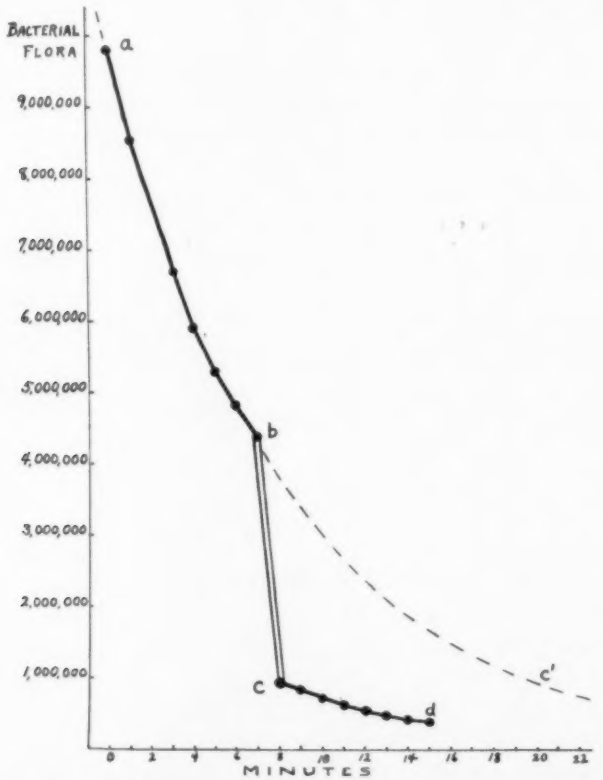

Chart 2.—Effect of 61 per cent alcohol (by weight) used with a brush. *ab*, the result of seven minutes of scrubbing with water; *bc*, the result of brushing the skin with the alcohol; *cd*, scrubbing resumed. *bc* is equivalent to *bc'*, or thirteen and one-third minutes of scrubbing.

GERMICIDAL POWER OF ALCOHOL IN VITRO

The experiments reported indicate more surely than any test tube findings what actually happens to the bacterial flora when alcohol is applied to skin. Nevertheless, a better understanding of the mechanism of cutaneous disinfection and the rational use of alcohol in surgical technic requires some definite knowledge of what alcohol does to bacteria in vitro.

Results obtained by Beyer (1911), Gregersen (1916) and Christiansen (1918) are shown in table 3. All three workers used dried Staph. aureus on threads or garnets. All used alcohol by weight per cent, thus avoiding a serious error of earlier, and not a few subsequent,

TABLE 3.—*Time Required by Different Solutions of Alcohol to Kill Staphylococcus Aureus in Vitro (After Christiansen; Adapted)*

	Time Required for Sterilization				Time Required for Sterilization		
Alcohol, Weight, %	Beyer, Minutes	Gregersen, Minutes	Christiansen, Minutes	Alcohol, Weight, %	Beyer, Minutes	Gregersen, Minutes	Christiansen, Minutes
30	..	300	35	70	½	¾	½
40	>60	37	5	80	22	2	¼
50	47	5	1	90	>60	22	½
60	12	1½	¾	100	..	(>7 days)	>60

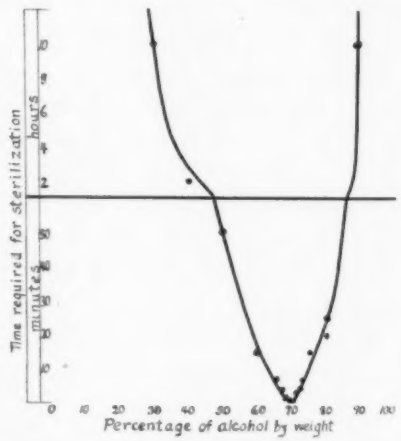

Chart 3.—Sterilizing power of solutions of alcohol in vitro. Beyer's results in graphic form.

investigators. All performed their experiments at "room" temperature. Beyer's work is of special interest, and his results when put in graphic form (chart 3) are striking.

It must be kept in mind, however, that all these results are compiled from end point determinations. They leave out of consideration altogether the rate of degermation, a matter of prime importance when applied to cutaneous disinfection. The easy assumption that there exists a close and constant relation between velocity of germicidal action and the time required for complete sterilization is as yet unsupported by experimental evidence.

In a fresh study of this problem use was made of a new quantitative test with bacteria in suspension.

Method.—The test organisms used were Bacillus coli communis, Staph. aureus and Staphylococcus albus, the first two from laboratory stock cultures and the last isolated from my own skin. The organisms were subcultured in infusion bouillon at 37 C. for twenty-four hours. From 1 to 5 cc. of the subculture was added to 100 cc. of sterile distilled water, and this suspension was shaken with beads in a mechanical shaker for twenty minutes or more.

Alcohol: Solutions were prepared with absolute alcohol and distilled water by actual weight.

Technic of Test: Three cubic centimeters of the alcohol solution to be tested was put in a sterile teaspoon, which was held over a beaker containing 197 cc. of sterile distilled water. One capillary drop (0.012 cc.) of the bacterial suspension was added to the alcohol. At the end of the test period, bacteria and alcohol were precipitated into the water below, and the mixture was stirred

TABLE 4.—*Quantitative Study of the Effects of Alcohol on Test Bacteria in Suspension*

Length of Exposure, Seconds	B. coli				Staph. albus			Staph. aureus	
	30% Alcohol	60% Alcohol	70% Alcohol	80% Alcohol	1% Alcohol	50% Alcohol	70% Alcohol	64% Alcohol	70% Alcohol
0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1	....	....	54.7	....	....	....	15.5	....	3.3
3	....	....	7.0	....	....	....	16.8	32.0	0.3
5	....	....	4.5	....	....	....	8.6	....	....
6	....	....	....	....	....	....	....	36.0	....
9	....	....	....	....	....	....	....	18.0	....
10	....	....	5.8	35.0	....	....	13.0	....	0.7
15	13.6	....	0.6	....	....	....	17.7	....	0.0
18	....	....	....	....	....	....	....	14.0	....
20	11.5	....	1.6	2.0	....	....	7.7	....	....
21	....	....	....	....	....	....	....	11.0	....
25	9.1	....	0.1	....	....	....	0.02	....	....
30	9.7	....	....	0.0	....	....	....	....	0.0
35	....	....	....	....	....	....	0.07	....	....
40	....	4.0	0.0	0.0	....	....	....	....	....
50	....	....	....	0.0	....	....	....	....	....
60	....	0.0	....	0.0	....	0.0	0.0	....	....
90	....	0.0	....	....	....	0.0	0.0	....	....
120	....	0.0	....	....	....	0.0	0.0	....	....
1200	....	....	....	....	79.0	....	....	....	....

Results are expressed in percentages of surviving organisms. The solutions of alcohol were prepared by the weight-percentage method.

thoroughly with the spoon. The exceedingly rapid diffusion of alcohol in the water is depended on to bring its lethal action to an abrupt termination. Several 1 cc. specimens were taken at once for plating and culture. Controls were observed of the water used, of capillary drops of suspension in 200 cc. of water without alcohol and of capillary drops added after the 3 cc. of alcohol had been put in the 197 cc. of water. (These showed that the alcohol after dilution had no bactericidal or bacteriostatic effect.)

Results.—Results are summarized in table 4. It is admittedly an incomplete study. Several important points regarding the germicidal power of alcohol are brought out by it, nevertheless.

1. Alcohol in proper concentrations is a powerful germicide when in contact with these test organisms in suspension.

2. Alcohol destroys (vegetative) bacteria in aqueous suspension at a constantly diminishing rate. This rate does not appear to be regularly

logarithmic throughout (as in the case with mercury bichloride or phenol); there is a sharp immediate reduction, after which the process takes place more slowly.

3. Of the solutions tested, 70 per cent solution (by weight) is the most rapidly bactericidal. Even 1 per cent alcohol, however, kills these test bacteria slowly.

4. Susceptibility to alcohol varies with different kinds of bacteria. The 70 per cent solution appears to be toxic for Staph. aureus in particular. (It is interesting in this connection to recall that Beyer and others used only Staph. aureus as a test organism.)

In the test described, contact between alcohol and bacteria must be almost perfect, surely better than when bacteria are adherent to threads and garnets and far better than when they are concealed deep in crevices and irregularities of the skin. This degree of contact, I believe, explains why the bactericidal power of alcohol is greatest against bacteria in suspension, less when test organisms are attached to threads and garnets, still less when alcohol is rubbed on skin and least of all when alcohol is applied to skin without friction.

ALCOHOL AS A FAT SOLVENT

As has been indicated, alcohol was employed by operators at first solely because of its supposed fat solvent action, and to this day most surgical textbooks recommend its use for that reason. Suspicions as to the accuracy of this view were first aroused when I was unable to recover viable organisms from alcohol in which hands and arms had been washed.

A variety of fats may be encountered on the skin, some of which are collected by contact with greasy or oily objects and others of which are supplied by secretions of the skin itself. The former group is made up chiefly of grease from food and of hydrocarbons which abound in a machine age. Indigenous fats come from the sebaceous glands, which secrete an oily liquid that "sets" on exposure to air. Its exact composition is not known, but it contains fats, soaps, cholesterol, albuminous material, epithelial cells and inorganic salts (Howell,[19] 1924).

To represent this collection of fats I have chosen for the purposes of study: (*a*) petrolatum, a typical hydrocarbon, (*b*) olive oil, almost pure olein, and (*c*) hydrous wool fat, a typical ester of cholesterol. The results of solubility tests are, briefly:

1. Petrolatum is practically insoluble in cold alcohol.

19. Howell, W. H.: Textbook of Physiology, Philadelphia, W. B. Saunders Company, 1924, p. 883.

2. At room temperature, 1 part of olive oil is found to be completely dissolved in 65 parts of pure alcohol in three minutes, in 325 parts of 95 per cent (by volume) alcohol in eight minutes and in 650 parts of 80 per cent (by weight) alcohol in ten minutes. The amount of olive oil dissolved by 650 parts of 70 per cent (by weight) alcohol after four hours' contact is scarcely detectable.

3. Hydrous wool fat is insoluble in ethyl alcohol.

It seems clear, therefore, that in its strongly germicidal concentrations alcohol is not a fat solvent and that its disinfecting action on skin must be largely or entirely independent of such a property.

PREPARATION AND EFFECTIVE USE OF GERMICIDAL SOLUTIONS OF ALCOHOL

Concentration of alcohol in solutions is by no means simple. Accurate preparation of solutions of alcohol and, conversely, determination of the concentration of alcohol in any given aqueous solution, are complicated by three variables, i. e., specific gravity, temperature expansion, and reaction contraction.

One cubic centimeter of pure distilled water at 4 C. weighs exactly 1 Gm. Since water expands only slightly on heating, this relation between volume and weight remains practically unaltered by variations in temperature, so that quantities of water may be measured by volume or weight interchangeably and fairly accurately. Not so with alcohol. Alcohol is lighter than water; so 1 cc. weighs less than 1 Gm. And because alcohol is very expansile, 1 cc. of warm alcohol weighs less than 1 cc. of cold alcohol. The same is true of any solution of alcohol, to a degree depending on the relative proportion of the ingredients. Preparation of exact concentrations of alcohol by volume is further complicated by the fact that 1 cc. of water plus 1 cc. of alcohol comes to less than 2 cc. of the mixture, for a contraction takes place with production of heat, a contraction which becomes even more pronounced as the solution cools.

Concentration of alcohol may be expressed either as volume per cent or as weight per cent. Volume per cent indicates the number of cubic centimeters of pure alcohol in each 100 cc. of solution. Weight per cent indicates the number of grams of pure alcohol in each 100 Gm. of solution.

Seventy per cent alcohol by volume is commonly prepared as follows: Seven hundred and thirty-seven cubic centimeters of commercial (approximately 95 per cent) alcohol ($\frac{700}{0.95}$) is added to water sufficient to make 1,000 cc. But the weight content of pure alcohol in such a solution is uncertain, owing to variations in the concentration of different lots of

commercial alcohol, to variations in the temperature of alcohol when measured and to the different effects of measuring the water before adding it to the alcohol and of simply adding water up to the 1,000 cc. mark. It is easy to see, therefore, how the bactericidal action of any given solution of alcohol prepared by volume might vary widely from time to time and would be unpredictable even when employed in tests at a standard temperature. Seventy per cent alcohol by weight, on the other hand, prepared by combining 700 Gm. of pure alcohol and 300 Gm. of distilled water, is a uniform preparation having definite and constant bactericidal effect.

Failure of many investigators to appreciate these characteristics of alcoholic solutions or even to recognize the difference between per-

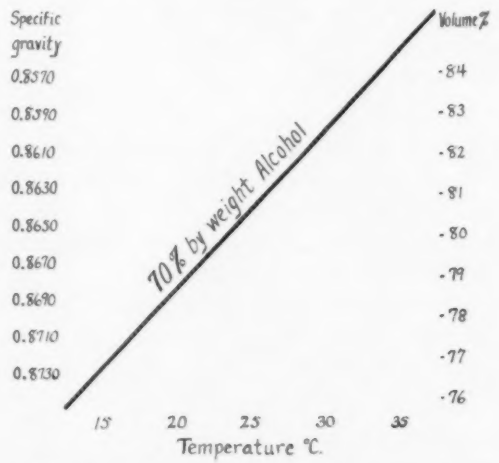

Chart 4.—Chart which may be used with an alcoholometer in preparing 70 per cent alcohol (by weight) from commercial or other solutions of alcohol.

centages by volume and by weight makes it necessary to discount their conclusions as to the germicidal power of alcohol. And because alcohol has so narrow a range of effective bactericidal concentration, surgeons are well advised to keep these points clearly in mind.

In practice it is not feasible actually to weigh out the ingredients of solutions of alcohol. Besides, for the sake of economy one must use commercial instead of pure alcohol. It is possible, though troublesome, to prepare weight per cent solutions from commercial alcohol with the help of a hydrometer, a thermometer and appropriate tables. To be perfectly accurate such solutions should be prepared at the temperature at which they are to be used. To simplify the matter I have prepared and used with great satisfaction a chart (chart 4) which enables one after a little practice to prepare 70 per cent alcohol by weight from

commercial alcohol quite easily. The University Hospital (Tsinan) has for several years employed large, finely graded alcoholometers which have thermometers incorporated within them. One of these is used by the pharmacist in preparation of stock 70 per cent solution; another is kept in the operating room, where a duty of the supervising nurse is to restore used and filtered alcohol to full (70 per cent) strength by the addition of either commercial alcohol or water as may be required.

In operating rooms and physicans' offices, where time or facilities may be lacking for such measurements, 70 per cent by weight can be approximated by taking 810 cc. of commercial (95 per cent) alcohol at operating room temperature (25 C.; 77 F.) and adding cold distilled water to bring the total volume of the solution to 1,000 cc.

Evaporation of alcohol is a matter of practical importance. Pure alcohol is hydroscopic; when exposed to air it gradually approaches 95 per cent. Aqueous solutions of alcohol vaporize by giving off two fractions, 95 per cent alcohol and water. Thus commercial alcohol allowed to evaporate to half its volume will still be 95 per cent. Solutions less than 95 per cent became progressively weaker when exposed because the 95 per cent alcohol content, having a higher vapor pressure than the water fraction, passes off more quickly. Seventy per cent alcohol (by weight) evaporated to half its weight will be found changed to 62 per cent and to have lost most of its germicidal power in the process. This characteristic renders heated alcohol impractical for disinfection of the hands, even though the higher temperature might at first increase the bactericidal activity. And since even slight variations from 70 per cent lessen the disinfectant power of alcohol, it is advantageous to keep solutions covered when not in use.

The quantitative method which has been used in this study may be readily adapted to measure accurately the total bactericidal effect of any routine procedure of preoperative disinfection of the hands. In 1933 I visited eight well known surgical clinics in the United States and abroad, where I was permitted to observe carefully the technic used in operating rooms, both in theory and in practice. From my quantitative studies (those on other germicides than alcohol to be published in the near future) it was estimated that disinfection of the hands as taught and practiced in these clinics resulted in reduction of bacteria to between 50 and 10 per cent of the original flora. That is to say, operators were regularly putting on gown and gloves with as many as 5,000,000, and perhaps not often less than 500,000 organisms, still on their hands and arms.

On the basis of laboratory results, subsequently checked by clinical experience, the following routine is recommended for preoperative preparation of hands and arms. It is a simple method, but it is efficacious in reducing the bacterial flora provided it is followed closely.

1. Scrub the hands and arms thoroughly with a brush, soap and warm water for at least seven minutes. Time taken to trim and clean the nails should not be counted. The effect of such a toilet is to remove practically all ordinary grease and dirt, as well as "foreign" bacteria, and to reduce the "native" skin flora by slightly over 50 per cent.

2. Dry well with a sterile absorbent towel. This step, I have discovered, does not wipe off many bacteria, but it is necessary in order to avoid carrying water into the germicide and changing its concentration.

3. Rinse the hands and arms briefly in 95 per cent alcohol to remove any remaining water. This part of the procedure has relatively little germicidal effect; so there is no advantage in prolonging it. The 95 per cent alcohol carried over into the next basin is helpful rather than otherwise, for it tends to counteract the weakening effect of evaporation on 70 per cent alcohol.

4. Wash the hands and arms in a basin well filled with 70 per cent alcohol (by weight) which has been carefully and freshly prepared. A sterile piece of gauze or a washcloth should be used, and the skin should be rubbed firmly with the germicide. Time is important at this stage. I recommend a full three minutes by the clock. That will reduce the flora, as indicated in table 2 (experiment 8) to about 3 per cent of its former size, or approximately 1.5 per cent of that present before scrubbing was started.

5. Put on gown and gloves. If dry gloves are used, the hands will have to be dried, of course, with a second sterile towel.

The same basinful of 70 per cent alcohol should not be used for too long a period or by too many persons.

Used alcohol, filtered and brought up to correct strength, has been found satisfactory for subsequent use.

The use of 70 per cent (by weight) alcohol is recommended also in preparing the patient's skin for operation. Friction with a gauze sponge increases the germicidal effect. The alcohol should not be followed too quickly by ether, for time is an all-important factor in disinfection.

In another series of experiments, which will be reported separately, alcohol in 70 per cent (by weight) solution was found effective in disinfecting contaminated hands.

SUMMARY

By new quantitative methods, the germicidal power of solutions of ethyl alcohol have been tested, the important difference between concentrations by volume per cent and concentrations by weight per cent being kept in mind.

When used properly, alcohol is an exceedingly efficient germicide, both on skin and against vegetative bacteria in vitro. Exactly 70 per

cent by weight (which has no constant volume per cent equivalent) is the most effective concentration. Even slight variations from this particular strength lessen the bactericidal power of the solution. Seventy per cent by volume is almost useless.

Degermation (a more accurate term than "disinfection") of skin by alcohol takes place at a regularly logarithmic rate. Each minute the skin is kept in 70 per cent (by weight) solution without friction is equivalent to about six and one-half minutes of scrubbing in water. Friction increases the speed of degermation.

This effect is due to inherent bactericidal action and not to any detergent properties, for in its strongly germicidal concentrations alcohol is not a fat solvent.

Against test bacteria in suspension 70 per cent (by weight) alcohol acts even more strongly and rapidly. Higher and lower concentrations are less effective. The rate of degermation of suspensions in vitro does not seem to be regularly logarithmic; there is a large instantaneous drop, followed by more gradual diminution in numbers of surviving organisms.

The difference between the degerming effects of alcohol on skin and in vitro are thought to be due largely, if not entirely, to differences in degree of contact between germicide and bacteria. This explains also why friction increases the germicidal action of alcohol on skin.

Evaporation weakens 70 per cent alcohol and lessens its bactericidal power sufficiently to make this a matter of practical importance.

Difficulties in making accurate solutions of alcohol are discussed, and a relatively simple method of preparing a 70 per cent by weight concentration from commerical alcohol is described.

On the basis of these experimental findings, a routine method of preoperative preparation of the hands has been evolved which, while simple, is a great deal more effective than technics in use at present in many leading hospitals. This procedure has been employed with satisfaction in my operating room for the last four years and, having passed that clinical test, is now recommended to others.

Seventy per cent by weight alcohol is recommended also for use in preparing the field of operation and in disinfecting contaminated hands.

Why exactly 70 per cent should be more toxic for bacteria than any other concentration of alcohol remains an interesting biochemical problem.

PARATHYROIDECTOMY FOR RAYNAUD'S DISEASE AND SCLERODERMA

LATE RESULTS

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AND

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NEW YORK

In a preliminary report,[1] published in 1935, we described 6 cases of Raynaud's disease and scleroderma treated by parathyroidectomy. At a later date,[2] one of us (J. H. G.) described 2 additional cases. The first report (by J. H. G.), which dealt with the technic of the operation, appeared in the *Journal of the Mount Sinai Hospital* for November 1937. Up to the present writing, the operation has been done in 17 cases. It is our present purpose to appraise the late results in these cases and to state the conclusions which this investigation has led us to form.

It may not be amiss to review briefly certain considerations which led to the rationale of our procedure.

Five years ago we were confronted with a case of generalized scleroderma. The patient was a man who was totally disabled by the disease. We used numerous therapeutic measures without effect, except that the accompanying symptoms of Raynaud's disease in the hands and feet were somewhat improved after calcium therapy. Selye had produced sclerodermatous changes in young rats by the intraperitoneal injection of parathyroid extract. We repeated his experiments on both rats and mice and confirmed his results. As a clinical experiment, therefore, parathyroidectomy was performed on the patient with scleroderma. The result encouraged us to treat other patients in a similar way.

In an effort to understand the mechanism underlying the production of scleroderma by the administration of parathyroid extract we have endeavored to interpret some of the factors in this complex problem.

From the Department of Surgery, New York Hospital and Cornell University Medical College, and from the Surgical Service of Dr. John H. Garlock, Mount Sinai Hospital.

1. Bernheim, A. R., and Garlock, J. H.: Parathyroidectomy for Raynaud's Disease and Scleroderma: A Preliminary Report, Ann. Surg. **101**:1012 (April) 1935.

2. Garlock, J. H.: Parathyroidectomy for Raynaud's Disease and Scleroderma, S. Clin. North America **16**:771 (June) 1936.

Apparently the main function of the parathyroid glands is to control calcium and phosphorus metabolism. This function is accomplished chiefly by mobilization of calcium and phosphorus from the bones. Excessive activity of the parathyroid glands results in decalcification of the bones.

Two forms of hyperparathyroidism are well recognized: (1) that seen in von Recklinghausen's disease, or generalized osteitis fibrosa cystica, in which an adenoma of the parathyroid is commonly found, and (2) the form described by Albright and his co-workers,[3] in which there is diffuse hyperplasia of the glands accompanied by recurring nephrolithiasis. Removal of the adenoma in the first instance and partial parathyroidectomy in the second are effective methods of treatment. A third form of disturbance of parathyroid function has been noted, namely, the hyperplasia frequently associated with rickets and osteomalacia.[4] In these conditions the calcium stores of the body are depleted as a result of deficient intake or absorption, and the parathyroid glands apparently must increase their activity in order to withdraw sufficient calcium from exhausted stores to supply the needs of the blood. This compensatory overactivity may be regarded as a work hypertrophy.

Diets low in calcium are common among adults, and the conditions which govern the absorption of calcium are frequently faulty. Accordingly, various degrees of calcium deficiency may occur, presumably accompanied by corresponding changes in the bones and in the parathyroid glands. It is noteworthy that the total calcium content of the blood is remarkably constant even when the calcium intake is low for a long period. Lennox [5] and his co-workers showed that there was no reduction from the normal calcium content of the blood of subjects starved for twenty-one days. It is therefore obvious that this constancy is maintained by the bones rather than by the diet, which is variable and intermittent. Furthermore, from all the evidence available it seems that the calcium furnished to the blood by the bones is always excreted and is not redeposited in the bones. There is apparently no reversible internal circulation of calcium such as exists, for example, in the case of the bile salts. On the other hand, the calcium absorbed from the intestinal tract is deposited in the bones. The mechanism of this difference in behavior is not clear. That there may be other physiologic

3. Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Studies on the Physiology of the Parathyroid Glands, Renal Complications of Hyperthyroidism, Am. J. M. Sc. **187**:49 (Jan.) 1934.

4. Cantarow, A.: Calcium Metabolism and Calcium Therapy, Philadelphia, Lea & Febiger, 1933, p. 104.

5. Lennox, W. G.; O'Conner, M., and Bellinger, M.: Chemical Changes in the Blood During Fasting in the Human Subject, Arch. Int. Med. **38**:553 (Nov.) 1926.

differences between absorbed calcium and calcium from the bones is suggested by clinical results. For example, the pain caused by muscle spasm in certain persons taking a diet low in calcium but having normal blood calcium is frequently dramatically relieved when a diet containing an adequate amount of the element is given. No detectable rise in blood calcium occurs.

Calcium exists in at least two forms in the blood: (1) that bound to protein (nondiffusible) and considered physiologically inactive, and (2) the diffusible, physiologically active or so-called "available" calcium. Some investigators are of the opinion that there are three or even four forms of calcium in the blood. It is possible that these different forms may vary in amount without reflecting changes in the total quantity. This phase of calcium metabolism is unexplained. But it is known that if the diffusible calcium is reduced in amount, as it is in the presence of tetany, muscular irritability is increased. This behavior may be considered the reaction of muscle tissue to the fundamental effect of calcium on cell permeability. For normal function, cells are dependent on the presence in their surrounding mediums of certain electrolytes, chiefly calcium, sodium and potassium in balanced proportions. Calcium has a consolidating, stabilizing effect on colloidal systems, so that it may be said to reduce the permeability of cells. On the other hand, sodium and potassium have a liquefying action on cell membranes and may be said to increase their permeability. Bayliss[6] has stated: "We have found reason to look on an increase of permeability of a membrane as an intimate part of the excitatory process, and inhibition, as the opposite process, would thus be associated with decrease of permeability." Thus, when calcium ions are reduced in the blood, cells may manifest increased excitability according to their function; for example, muscle cells would tend to overcontract and become spastic, while nerve cells would show increased irritability.

Obviously, in the reactions of the body to a decrease or lack of essential substances, the constitutional factor plays an important role. The constitutional factor may be considered a local hypersensitivity or inferiority which renders tissues more susceptible to unfavorable environment. As a result of observations covering a number of years, one of us (A. R. B.) formed the opinion that in certain persons a continued calcium deficiency may increase a predisposition to vasospasm. In diseases in which some of the symptoms are due to vasospasm, relief in a large number of cases has followed the use of a diet adequate in calcium.

It is our concept that in cases in which the disease responds to calcium treatment the parathyroid glands are relieved of their extra

6. Bayliss, W. M.: Principles of General Physiology, ed. 3, London, Longmans, Green & Co., 1920, p. 426.

work of drawing calcium from the bones and may return to a normal physiologic state. However, in certain instances improvement does not take place in spite of prolonged and intensive treatment. In such cases more or less permanent change may have occurred (permanent hyperplasia or disturbed function of the parathyroid glands); hence removal of one or more of these bodies seems indicated.

It seemed conceivable to us that vasospasm, the occurrence of which in Raynaud's disease is well established, plays a role of like importance in scleroderma. Thickening of the skin produced by scar tissue with a large collagen component may well be the result of slow interference with the blood supply through constriction of the vessels of the skin and those of the adjacent subcutaneous tissues. In many cases symptoms of Raynaud's disease and scleroderma occur together, and because sclerodermal changes appear more frequently in the skin of the exposed parts of the body, such as the fingers, hands, forearms and face, the suggestion arises that cold is also a factor which aggravates a tendency to spasm. There is evidence to indicate that sclerodermatous changes develop in areas in which the superficial vessels run parallel to the surface of the skin.

In most cases of true hyperparathyroidism the calcium content of the blood is found to be elevated and the phosphorus decreased. In no case of this series did hypercalcemia occur. A possible explanation of this difference may be that in the former condition overactivity of the glands is the result of disease which disturbs the normal relation between the stores and the blood, whereas in the latter normal glands overwork to maintain a normal calcium level in the blood.

It may also be noted that the inorganic phosphorus content of the blood was elevated above normal in most of these cases. Speculation concerning the significance of this finding seems to throw no light on the problem. Phosphorus generally bears a reciprocal relation to calcium, but not invariably. The metabolism of calcium and phosphorus is complex and is by no means fully understood. In this reconsideration of the factors concerned with our rationale of procedure we have discussed only those which seem to us relevant to the subject.

The histories of the 17 cases are herewith briefly described.

REPORT OF CASES

CASE 1 (previously reported).—F. L., a man aged 53, was first seen March 20, 1933. There were symptoms of fourteen months' duration, principally thickening of the skin of the fingers, the hands and the face. The feet later became involved. In the latter part of the illness most of the skin of the body became stiff, dry and discolored. There was inability to chew solid food because he could not open his jaws. The patient had taken a diet low in calcium most of his life.

Examination showed extensive and severe scleroderma, most marked on the hands, the forearms, the arms and the face. There was flexion contracture of all

the finger joints; because of this the patient had been unable to work. The value for calcium was 10 mg., that for phosphorus 4.5 mg. and that for phosphatase 5.2 units per hundred cubic centimeters of serum. Oscillometric readings showed marked diminution at the ankles and wrists. There was no response to conservative therapy.

Other laboratory examinations gave negative results. Parathyroidectomy was performed October 20 at the New York Hospital. Four parathyroids were demonstrated; two were removed. Microscopic examination of the glands showed acute parathyroiditis with possible oxyphilic degeneration. The immediate postoperative result was excellent as to improvement in the color of the skin. A moderate amount of softening of the skin of the hands, the face and the forearms was sufficient to permit the resumption of work and the proper mastication of food.

Late Follow-Up.—A recent follow-up, five years after the operation, showed no extension of the disease. There was considerable softening of the skin of the forearms and face but no improvement in the flexion contractions of the finger joints. The result in this case should be classed as fair.

Case 2 (previously reported).—A. G., a woman aged 32, was admitted to the wards of the New York Hospital April 27, 1934, with a four year history of Raynaud's disease. The symptoms were aggravated by cold weather and emotional upsets. There was no evidence of scleroderma.

Examination showed the typical cold water response seen in patients with Raynaud's disease. Oscillometric readings were slightly below the normal variation. The value for calcium was 11.4 mg. and that for phosphorus 4.9 mg. per hundred cubic centimeters of serum.

Operation was performed in May (Andrus). Two parathyroid glands were removed. Microscopic examination of the excised glands showed scattered evidences of hyperplasia. Convalescence was uneventful. The immediate effect of the operation was dramatic. The color of the hands and fingers returned to normal, and the response to cold water was negative.

Late Follow-Up.—Examination four years after the operation showed that the patient had improved for a year after the operation. This improvement was followed by a gradual return of the symptoms noted before operation. At present there is the usual difficulty with cold weather, and the symptoms are aggravated by a continuous emotional upset at home. The result in this case must be classified as poor.

Case 3 (previously reported).—H. R., a woman aged 58, was admitted to the New York Hospital on May 7, 1934, with a history of symptoms of ten months' duration, consisting of swelling and tenderness of the fingers and thickening of the skin, involving the fingers, the hands, the face and the neck. This condition was associated with blueness of the fingers, especially aggravated during cold weather.

Examination showed thickened, dry skin on the fingers, the hands, the face and the neck. The usual color response followed immersion of the parts in cold water. The value for calcium was 10.2 mg., that for phosphorus 4.6 mg. and that for phosphatase 3.5 units per hundred cubic centimeters of serum. The basal metabolism was normal. The calcium tolerance test showed an unusual elevation of the serum calcium after fifteen minutes. Oscillometric readings showed marked diminution in the oscillations at the calf, the ankle, the foot, the arm and the wrist. Determination of the surface temperature showed lowering in the hands

and feet. Parathyroidectomy was performed on June 22. Two and two-thirds parathyroids were removed. Microscopic examination showed scattered areas of hyperplasia.

The immediate postoperative result was excellent. The cutaneous discoloration disappeared. The temperature of the skin showed an elevation of 3 degrees. Within a year, considerable improvement was noted in the scleroderma; the softening involved the fingers, the hands and the face.

Late Follow-Up.—The patient died of an intercurrent infection in 1936.

CASE 4 (previously reported).—M. M., a woman aged 33, was first admitted to the medical service of the Mount Sinai Hospital on Nov. 10, 1933. Symptoms of Raynaud's disease extended over a period of ten years, with involvement of the toes and fingers. For the past two years sclerodermatous changes involving the face, the hands and the fingers had been noted.

Examination showed scleroderma of the face, producing retraction of the lip and inability to close the mouth. The sclerodermatous process involved also the neck, the forearms, the hands and the feet. There was mottled blue discoloration of the toes and fingers. The value for calcium was 10.4 mg., that for phosphorus 4.9 mg. and that for phosphatase 1.9 units per hundred cubic centimeters of serum. Oscillometric determinations showed diminution at the forearms, the wrists, the legs and the fingers. Parathyroidectomy was performed on March 26, 1934. Four parathyroids were isolated, and two glands were removed. Histologically these were found to be normal.

The immediate postoperative response was excellent. The skin was considerably softened. The blueness of the fingers and toes disappeared. At no time was there evidence of tetany.

Late Follow-Up.—Recent examination, four and a half years after the operation, showed that the skin of the face had again become sclerodermatous. The improvement in the hands and feet had not been maintained. Discoloration of the fingers had returned. This result must be classed as a failure.

CASE 5 (previously reported).—R. F., a woman aged 50, was first seen on June 8, 1934, with a three year history of Raynaud's disease involving the hands and feet.

Examination showed rather extensive scleroderma, involving the face, the hands, the feet, the forearms and the legs, with blueness of the fingers and a marked lowering of the surface temperature. Oscillometric determinations showed diminution at the ankles, the feet and the wrists. The cold water test produced the changes typical of Raynaud's disease. The value for calcium was 9.9 mg., that for phosphorus was 3.8 and that for phosphatase was 2.1 units per hundred cubic centimeters of serum. Parathyroidectomy was performed at Mount Sinai Hospital on July 18. Two and two-thirds glands were removed. Histologic examination of the glands showed isolated areas of hyperplasia. Convalescence was uneventful. Immediate improvement in the color of the fingers was noted.

Late Follow-Up.—Four years after the operation the skin of the face, the forearms, the hands and the legs had assumed a normal texture and appearance. It was soft and pliable and did not interfere with motion of the fingers. The patient noticed moderate blueness of the finger tips in cold weather. So far as the scleroderma was concerned, the result was excellent. The improvement in Raynaud's manifestations was fair.

CASE 6 (previously reported).—E. A., a woman aged 34, was seen in June 1934. She complained of pain in the hands and legs, of nine years' duration. She

had always been sensitive to cold weather. During the past five years, symptoms developed which were typical of Raynaud's disease. She also presented symptoms strongly suggesting disease of the coronary arteries.

Examination gave essentially negative results except for diminution in the surface temperature of the hands and feet, blue discoloration of the hands and feet and the typical response seen in patients with Raynaud's disease on immersion of the parts in cold water. Oscillometric examination showed diminution in the thigh, the calf, the ankle, the foot, the arm and the wrist. The value for calcium was 9.5 mg., that for phosphorus was 4.3 mg. and that for phosphatase was 1.7 units per hundred cubic centimeters of serum.

After careful study, the diagnosis of Raynaud's disease with probable spasm of the coronary artery was made.

Parathyroidectomy was performed at the New York Hospital on July 21. Four enlarged parathyroid glands were found. Two were removed in toto, and one was subtotally resected. Histologic examination of the excised glands revealed well defined hyperplasia.

The immediate postoperative response was excellent. The blueness of the fingers and toes disappeared.

Late Follow-Up.—Recent examination, four years after the operation showed that the patient occasionally had blueness of the finger tips in cold weather. She volunteered the information that the operation had resulted in marked improvement as far as the subjective complaints were concerned. She had gained considerable weight and was able to carry out her household duties. From our standpoint, the result in this case should be marked fair.

CASE 7 (previously reported).—M. S., a woman aged 27, was admitted to the Mount Sinai Hospital on May 14, 1935, with a history of Raynaud's disease of one year's duration and of sclerodermatous changes involving the hands and face of two months' duration. She lost 25 pounds (11.3 Kg.) in weight.

Examination showed a masklike expression of the face, caused by the scleroderma. There was involvement of the skin of the fingers and hands, with blue discoloration. There was diminution in surface temperature as compared with the normal. There was considerable diminution in the oscillometric readings at the calf, the ankle, the arm and the forearm. The value for calcium was 10.8 mg. per hundred cubic centimeters of serum; that for phosphorus was 4 mg. The cold water test produced a response characteristic of Raynaud's disease. Capillaroscopic studies of the nail beds showed thin capillary limbs, with spasm and hemorrhage.

Parathyroidectomy was performed on June 2. Four parathyroid glands were isolated. Two were removed in toto and one subtotally. Histologic examination showed no abnormalities. The immediate postoperative response was excellent. Capillaroscopic studies showed marked improvement.

Late Follow-Up.—Recent examination, three years after the operation, showed that the skin of the face, the hands and the fingers had resumed its normal appearance. The patient stated that in cold weather a slight blueness could be noted in the finger tips. The result in this case should be considered excellent.

CASE 8 (previously reported).—A. D., a woman aged 35, was admitted to the Mount Sinai Hospital on Jan. 4, 1936, with a history of Raynaud's disease of three years' duration, associated with pain. During the past six months sclerodermatous changes had been noted in the skin of the face and hands.

Examination showed masklike facies caused by scleroderma of the skin of the face, blueness of the fingers and atrophy of the pulp of the right middle finger, caused by an old infection. Scleroderma of the hands and fingers was marked. The value for calcium was 10.8 mg. and that for phosphorus 3.3 mg. per hundred cubic centimeters of serum. The basal metabolism was normal. Oscillometric determinations were slightly below normal. Dermatherm readings of the skin showed considerable diminution in the surface temperature of the fingers and hands. Immersion of the parts in cold water produced a typical attack of local asphyxia accompanied by severe pain in the fingers. Capillaroscopic studies revealed elongated capillary loops with sluggishness of the blood flow, amounting to complete stasis in some areas.

Parathyroidectomy was performed on January 15. Three parathyroids were isolated, two of them being considerably enlarged. Two glands were removed in toto, and half of the third was excised. Histologic examination showed what was thought to represent hyperplasia.

The immediate postoperative response was excellent. The blueness of the fingers disappeared, and no change occurred after immersion in cold water. There was a marked improvement in the surface temperature readings.

Late Follow-Up.—The patient was seen recently, two years after the operation. The skin of the face had returned to its normal state. The masklike expression had disappeared, and the wrinkles in the skin had returned. Slight change was noted in the finger tips. Otherwise the skin of the hands seemed normal. The patient volunteered the information that slight blueness of the finger tips was noted in cold weather. The result in this case should be classed as excellent for scleroderma and fair for Raynaud's symptoms.

Case 9.—D. P., a girl aged 19, was admitted to the Mount Sinai Hospital on Sept. 1, 1934, with a history of Raynaud's disease extending over a period of three and a half years. This was followed by thickening of the skin of the hands, the elbows, the forearms, the shoulders and the legs. A cervical ganglionectomy had been performed at the Mayo Clinic one year before, with improvement in the color of the skin on the side on which operation was done but not of the sclerodermatous process.

Examination showed an emaciated girl with generalized scleroderma involving most of the skin of the body, with contractures of the elbows, the shoulders and the hands. There was extensive involvement of the face, with retraction of the lips. Roentgenograms of the skeleton showed generalized osteoporosis. Determinations of the surface temperature showed diminution in the temperature of the fingers, the toes and the knees. The value for calcium was 10.2 mg., that for phosphorus was 4.3 and that for phosphatase was 2.2 units per hundred cubic centimeters of serum.

Parathyroidectomy was performed on October 9. Four parathyroids were isolated, two of which were enlarged to three times the normal size. Three glands were removed. Histologic examination showed focal inflammation in one gland.

During the succeeding few months the patient gained considerable weight, but no change was noted in the sclerodermatous process.

Late Follow-Up.—Recent examination, three and one-half years after the operation showed a marked improvement in the scleroderma. The skin of the face, the neck, the forearms and the hands was definitely softer. The contractures of the elbows and shoulders had disappeared. The patient stated that her condition had been much improved by the operation and that she had been able to resume a great many of her activities.

In the latter part of March 1938 the patient was again admitted to the Mount Sinai Hospital, with severe acute glomerular nephritis, to which disease she succumbed a week after admission.

CASE 10.—J. W., a woman aged 34, was admitted to the Mount Sinai Hospital on Jan. 26, 1937, with a history of Raynaud's disease extending over a period of ten years. Thyroidectomy had been performed for toxic goiter in 1923. The symptoms of Raynaud's disease were worse during cold weather and were also aggravated by numerous psychic disturbances. Scleroderma involving the fingers, the hands and the face had been present for two years.

Examination showed thickening of the skin of the face, the hands and the fingers. The thyroid gland was enlarged by reason of the presence of a number of adenomas in both lobes. The values for calcium and phosphorus were normal. The cold water test revealed a response typical of Raynaud's disease.

Parathyroidectomy was performed on February 5. The operation was made difficult by the presence of multiple adenomas of the thyroid and also by scar tissue from the previous thyroidectomy. In spite of this, four parathyroid bodies were demonstrated. Two of them were slightly enlarged; these were removed in toto, and another was subtotally resected. In addition, a thyroidectomy was performed.

The immediate response was not as dramatic as that seen in previous cases. However, there was a definite improvement in the blue discoloration of the fingers, which was a prominent symptom before operation.

Late Follow-Up.—Recent examination, one year after the operation, showed that the thickening of the skin had practically disappeared, especially in the face. The skin of the fingers and hands was considerably softer. However, the changes in color noted before operation were still present. From the standpoint of the scleroderma the result in this case was excellent. The symptoms of Raynaud's disease, however, were not influenced by the operation.

CASE 11.—E. S., a woman aged 40, was admitted to the Mount Sinai Hospital on Dec. 31, 1935. The history was that of Raynaud's disease of the hands and feet, extending over a period of eight years, with aggravation of the symptoms during cold weather. During the past five years the patient had had recurring infections of the fingers, involving the pulp. For the past three years there had been thickening of the skin of the face, producing a masklike appearance, and thickening of the skin of the fingers and hands. Considerable atrophy of the pulp of most of the fingers was noted. Oscillometric determinations were normal. The temperature of the skin was not affected. The value for calcium was 12.5 mg. and that for phosphorus 4.1 mg. per hundred cubic centimeters of serum.

Parathyroidectomy was performed on Jan. 28, 1936. Two parathyroid glands were demonstrated. They were slightly enlarged. These were removed in toto. Histologic examination showed increase in the eosinophilic cells.

The immediate response after operation was satisfactory. The blueness of the fingers disappeared and was replaced by the normal pink.

Late Follow-Up.—A recent check-up examination, two years after the operation, showed that the scleroderma of the face, the fingers and the hands had been considerably improved. However, color changes involving the fingers were still present, although not to the extent noted before operation. The result in this case from the standpoint of the sclerodermatous process may be classed as good, and from that of Raynaud's symptom as fair.

Case 12.—A. H., a woman aged 26, was admitted to the Mount Sinai Hospital on May 28, 1937. The history of symptoms extended over ten years, during which time she had noted a gradual tightening of the skin of the fingers and hands. The tightness had become progressively worse and had been more marked during the last five years. During cold weather blueness of the fingers was noted. The disease finally involved the face, the neck, the upper part of the chest, the forearms, the hands and the feet.

Examination showed extensive scleroderma in the regions enumerated, with atrophy of the fingers and impairment of function in the finger joints. The lips were retracted so as to expose the upper and lower teeth. All examinations of the blood gave negative results. The value for calcium was 10.6 mg. and that for phosphorus 3.5 mg. per hundred cubic centimeters of serum.

Parathyroidectomy was performed on June 6. Two slightly enlarged glands were removed. Histologic examination revealed nothing of note.

Late Follow-Up.—The result in this case has been unusually good. Ten months after the operation the patient had gained 40 pounds (18 Kg.). The cutaneous thickening had almost completely disappeared. The patient was able to close the mouth, and normal function had returned in the fingers.

Case 13.—H. C., a man aged 38, was admitted to the Mount Sinai Hospital on Oct. 21, 1937, and discharged on November 20. The history of symptoms extended over six months, with thickening and tightening of the skin, starting at the fingers and extending to the arms, the legs, the face and the neck. In a short while the skin of the entire body became involved. This rendered locomotion difficult. The disease was accompanied by severe weakness. There were no changes in color.

Examination showed a chronically ill man with an extensive sclerodermatous process involving the entire body. The skin was tight and glazed, and there was atrophy of the musculature of the legs and forearms. All laboratory examinations gave negative results. The value for calcium was 10.6 mg., that for phosphorus was 2.9 mg. and that for phosphatase was 5 King Armstrong units per hundred cubic centimeters of serum. Oscillometric readings showed slight diminution in the legs. The urine contained no arsenic.

Two and one-half parathyroid glands were removed on November 4. The postoperative convalescence was smooth.

Late Follow-Up.—The patient was seen four months after the operation, at which time only slight improvement was noted.

Case 14.—W. D., a man aged 56, was admitted to the Mount Sinai Hospital on Jan. 18, 1938. The history of symptoms extended over a period of two years, with onset of thickening and tightness of the skin, beginning in the hands and wrists and finally involving the entire body. There was blueness of the finger tips, with pain in cold weather. The patient was compelled to give up his work as a letter carrier.

Physical examination showed an extensive sclerodermatous process involving the hands, the forearms, the face, the neck, the chest and the legs. There was limitation of motion in the finger joints. All laboratory examinations gave negative results. The value for calcium was 9.6 mg. and that for phosphorus 4.3 mg. per hundred cubic centimeters of serum.

Parathyroidectomy was performed on January 24. Four parathyroid bodies were isolated; two appeared to be about three times the normal size. Two glands were removed completely and one subtotally.

Follow-Up.—The patient was last seen two months after operation. At that time a noticeable improvement had taken place. There was distinct softening of the skin of the hands and face. Motion in the finger joints had improved. The final result cannot yet be ascertained.

CASE 15.—C. S., a woman aged 36, was admitted to the New York Hospital on Jan. 12, 1935, with Raynaud's disease of eight years' duration. The symptoms were typical of this disease and were more marked during cold weather. They consisted of the usual changes in color, accompanied by pain and involving the hands and feet. A few years before admission the tips of two fingers had become gangrenous.

Physical examination gave completely negative results. There was no evidence of scleroderma. A very thorough work-up revealed nothing of note. Values for calcium and phosphorus were normal. Estimations of the cutaneous temperature showed diminution in the temperature of the fingers and the feet.

Operation was done on January 16. Three slightly enlarged parathyroid glands were found; two were removed completely, and one was subtotally resected. Histologic examination of these glands showed nothing of note.

The immediate response was dramatic. Whereas before operation the cold water test produced definite changes of color in both the hands and the feet, postoperative immersion of the parts in cold water for as long as three quarters of an hour failed to reveal any deviation from the normal.

The improvement noted during the postoperative stay in the hospital continued for two or three months. Then all the symptoms returned.

Late Follow-Up.—The patient was recently examined, three years after the operation, and it was found that all the preoperative symptoms had returned. The result in this case should be classed as a failure.

CASE 16.—W. McD., a man aged 39, was admitted to the New York Hospital on May 2, 1935, with a history of scleroderma extending over one and a half years. The process originated in the feet and extended up the legs as far as the groins. The hands and forearms became involved at a later date. For two or three months before the patient's admission to the hospital, he had chronic ulcers on the dorsum of each foot, which refused to heal. The patient presented scleroderma of rather severe degree. An ulcer was present on the dorsum of each foot, measuring about 1 inch (2.5 cm.) in diameter. These were extremely painful. The value for calcium was 11.2 mg., that for phosphorus 4.1 mg. and that for phosphatase 1.4 units per hundred cubic centimeters of serum.

Operation was performed on May 15. Four slightly enlarged parathyroid bodies were demonstrated; two were removed in toto and one subtotally. Histologic examination of the glands showed "slight hyperplasia."

Follow-Up.—The patient improved slowly during the first six months.

Late Follow-Up.—The patient was seen two and a half years after operation, and examination at that time showed that the ulcers on the feet were completely healed. The patient had gained considerable weight, in certain parts of the body the scleroderma had improved considerably, and in others the process seemed to be stationary. The operation apparently had resulted in at least a halt of the disease. The result in this case may be classed as fair.

CASE 17.—F. B., a girl aged 16, was admitted to the New York Hospital on June 19, 1935, with a history of scleroderma of three months' duration. For two years preceeding her admission she had noted tingling of the fingers and feet, with

coldness and blueness in cold weather. Three months previously she had noted tightening of the skin of the hands, the fingers, the forearms and the feet.

Examination showed a poorly developed and poorly nourished girl, considerably underweight, with scleroderma extending over most of the body but especially severe on the hands, the feet and the neck. The cold water test elicited a positive response. The laboratory examinations gave negative results. Oscillometric readings showed a decrease at the ankles and wrists.

Operation was performed on June 22. Four parathyroid bodies were found. Three were removed in toto. Histologic examination of the glands showed infiltration with polymorphonuclear leukocytes, with the formation of what the pathologist interpreted as microscopic abscesses in two or three places.

Late Follow-Up.—The patient was seen two years after operation. She volunteered the information that cold weather no longer bothered her. There were few, if any, changes in color in the fingers.

Examination showed a softening of the sclerodermatous process. The patient had gained considerable weight and was better able to use her hands. The result in this case was classed as good.

COMMENT

We have examined the records and late results of parathyroidectomy in these 17 cases of Raynaud's disease and scleroderma. We have noted in the cases of Raynaud's disease in which the condition was not associated with sclerodermatous change that improvement followed immediately on the operation but did not continue. In all such cases the symptoms eventually returned. Improvement occurred in all cases of scleroderma and was maintained in all but 1. In a number of cases the greatest improvement in symptoms did not immediately follow the operation, as in the cases of Raynaud's disease, but occurred several months later.

From this experience we must conclude that parathyroidectomy should not be performed as the treatment for uncomplicated Raynaud's disease. In this respect we are reversing the opinion expressed in our original paper, published in 1935. If our original concept is correct, namely, that a like mechanism underlies the development of Raynaud's disease and that of scleroderma, it is difficult to explain this variation in the response of these two conditions to the operative procedure. On the other hand, however, we are of the opinion that improvement may be expected to follow parathyroidectomy in cases of scleroderma if the operation is performed in the early stages of the disease, before articular changes and contractures have developed. For obvious reasons, patients with such changes may not be expected to show any considerable improvement, but from our experience it seems that parathyroidectomy may bring about a halt in the progression of the disease.

There seem to be no contraindications to the operation. In none of the patients did symptoms of tetany develop at any time, nor were there any other postoperative complications. There was no mortality.

Criticism may be made that removal of the parathyroid glands may not have anything to do with the improvement noted and that such improvement may be attributed to the unintentional division of sympathetic nerve fibers during the dissection of the neck in the course of the operation. This explanation may possibly account for some of the immediate effects following the operation, before severed sympathetic fibers have had time to regenerate, and may well explain the short-lived, dramatic response in the cases of Raynaud's disease. However, a relation between the parathyroid glands and scleroderma is indicated in the experimental production of scleroderma through the use of parathyroid extract; so it seems fair to attribute the improvement in these cases to removal of the parathyroid glands.

CONCLUSIONS

From examination of the late results of parathyroidectomy in 17 cases we have concluded that the operation has no place in the therapy of Raynaud's disease. While the immediate results are impressive and often dramatic, the late results do not measure up to the expectations expressed in our original paper. However, in the treatment of scleroderma, whether the condition is generalized or confined to the hands and face, we are of the opinion that parathyroidectomy offers the patient the probability of recession of the disease in the early stages, and of halting of the process in the late ones. At present, no other method of treatment is known to us which offers this outlook to the patient suffering from scleroderma.

REGIONAL REDISTRIBUTION OF BLOOD IN EXPERIMENTAL SECONDARY SHOCK

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Implied in the concept of physiologic homeostasis (Cannon [1]) is the occurrence of translocations of blood in response to normal and urgent stimuli. Such movements of blood have been investigated in relation to certain regions of the body, particularly the spleen (Barcroft and others [2]) and the lungs (Hochrein and Keller; [3] David and Siedek [4]). The exact redistribution of blood in traumatic or hemorrhagic shock has been the subject of much debate. It is evident that the total mass of blood in any area is dependent on the local vascular tonus. That the tone of the blood vessels is altered by secondary shock is well known, but whether in the direction of vasodilatation or of vasoconstriction is not yet well established. The question is raised: Is the alteration of vascular tonus local or widespread? Accepting the observations of Goltz,[5] who showed that a state of splanchnic vasodilatation could be produced in the frog by repeated blows to the abdomen, Fischer [6] concluded that the phenomena of secondary shock might be explained on this basis. Attractive as the hypothesis was, it received little corroboration, as various clinical workers (Wallace, Drummond

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and Fraser [7]) failed to observe splanchnic vasodilatation in secondary shock. However, it has not as yet been tested experimentally, and proof of its incorrectness is based on circumstantial evidence. It has been suggested that, in contradistinction to this splanchnic "pooling" of blood, stagnation of blood occurs in dilated capillaries of the muscles (Starling [8]) as a result of muscular flaccidity and lack of movement. The fall of blood pressure in shock has been explained also by a loss of blood plasma through the walls of excessively constricted peripheral capillaries (Malcolm; [9] Erlanger and Gasser [10]). Peripheral vasoconstriction has also been observed by Seelig and Lyon,[11] while, more recently, peripheral vasodilation has been observed (Smith [12]). The perfusion rate through isolated vascular beds, e. g., the kidney, the bowel or the hindlimb, has been claimed to be diminished in secondary shock (Morison and Hooker [13]). Again, the phenomena of shock have been attributed to a loss of venous tone caused by failure of the venopressor mechanism (Henderson [14]). It is evident that much uncertainty still exists regarding the state of vascular tonus in shock. In the investigation reported here an effort has been made to determine the redistribution of blood in animals with secondary shock with particular reference to:

(*a*) Influence of trauma, hemorrhage, histamine and epinephrine.

(*b*) Presence or absence of splanchnic vasodilation.

(*c*) General or local alterations of blood vessel tonus.

METHODS

Healthy dogs weighing from 10 to 20 Kg. were used in these experiments. Anesthesia was induced by the intraperitoneal injection of pentobarbital sodium. The question arose as to the method to be used for measurement of the regional distribution of blood. In isolated vascular areas which are accessible, such as the hindlimb, kidney, liver, spleen and bowel, this may be determined by means

7. Wallace, C.; Fraser, J., and Drummond, H.: The Distribution of Blood in Traumatic Shock, Lancet **2**:727, 1917.

8. Starling, E. H.: Nature et traitement du shock chirurgical, Arch. méd. belges **71**:369, 1918.

9. Malcolm, J. D.: On the Condition of the Blood Vessels During Shock, Lancet **1**:497, 1907.

10. Erlanger, J., and Gasser, H. S.: Circulatory Failure Due to Adrenalin, Am. J. Physiol. **49**:345, 1919.

11. Seelig, M. G., and Lyon, E. P.: Further Experimental Data on the Vasomotor Relations of Shock, Surg., Gynec. & Obst. **11**:146, 1910.

12. Smith, M. I.: The Peripheral Vasomotor Mechanism in Experimental Shock, J. Pharmacol. & Exper. Therap. **34**:239, 1928.

13. Morison, R. A., and Hooker, D. R.: The Vascular Tone and the Distribution of the Blood in Surgical Shock, Am. J. Physiol. **36**:86, 1915.

14. Henderson, Y.: Acapnia and Shock, Am. J. Physiol. **21**:126, 1908.

of the plethysmograph. This procedure, however, is subject to two defects: (1) Quantitative studies are not accurate and (2) unavoidable handling of the region to be studied results in an alteration of the local vascular tone. Observation of the rate of flow of a perfusion fluid through a vascular area is a method which can give information limited to the state of local vascular tone, but it is incapable of yielding even approximate quantitative data regarding variations in the total amount of blood in that area (Morison and Hooker [13]). Observation of the exposed region, e. g., the spleen, by direct vision or roentgen rays is obviously inadequate (Barcroft and others [2]). However, direct observation of the cerebral blood vessels through a cranial "window" has yielded excellent qualitative results (Forbes [15]). All these methods have the defect that they are incapable of application to inaccessible areas, such as the lungs and heart. This disadvantage has been overcome to some extent by use of methods of measuring the variations in the rate of blood flow through vascular regions. Such are thermostromuhr method (Schmid;[16] Rein [17]), the balloon method (David and Siedek [4]) and its modification (Blalock and others [18]).

In order to estimate the redistribution of blood in the head, thoracic, splanchnic and peripheral areas the following method was devised. The head area was arbitrarily fixed as extending from the foramen magnum cephalad. The thoracic region was placed as between the clavicles and the xiphisternum, which was demonstrated by dissection to lie on the same sagittal plane as the domes of the diaphragmatic musculature. The abdominal area was placed as between the xiphisternum and the iliac crests. Finally, the peripheral region was determined as lying caudad to the iliac crests and comprising both hindlimbs. The animal was suspended in a frame, from the cross bar of which hung a sensitive scale attached to a movable platform. The movements of the scale were recorded by means of a pulley-lever arrangement on a kymograph. The area to be weighed was placed on the platform, the remainder of the animal being adequately supported by wooden blocks. Because of the inertia imposed by the rigid vertebral column, calibration of the moving scale was performed with the animal in situ before and after each experiment. The animals were deprived of food for two days prior to each experiment, and the urinary bladder was emptied by catheter. This simple method possesses several advantages:

(*a*) The animal remains intact.

(*b*) There is no disturbance of the vascular bed of the area to be examined.

(*c*) Quantitative results are obtainable and can be recorded graphically.

The results after calibration of the scale were found to be accurate to within 5 Gm. It was found that the scale usually underestimated rather than overestimated the degree of change in weight. Therefore, the results are based on conservative calculations. Simultaneous readings of the blood pressure were obtained from the left carotid artery. Secondary shock was produced by trauma to the hindlimbs and by repeated hemorrhage.

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15. Forbes, H. S.: The Cerebral Circulation: I. Observation and Measurement of the Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

16. Schmid, J.: Die grösse des Blutstroms in der Pfortader, Arch. f. d. ges. Physiol. **125**:527, 1908.

17. Rein, H.: Die Thermo-Stromuhr, Ztschr. f. Biol. **87**:394, 1928.

18. Blalock, A., and Mason, M. F.: Observations on the Blood Flow and Gaseous Metabolism of Liver of Unanesthetized Dogs, Am. J. Physiol. **117**:328, 1936.

NORMAL REDISTRIBUTION OF BLOOD

The amount of blood in the head and peripheral areas, as evidenced by alterations in weight, remains remarkably constant under the conditions of these experiments. However, in the splanchnic and thoracic areas there occurs a rhythmic variation in the total quantity of blood (fig. 1). This is represented by a slow biphasic curve which is equivalent to a variation of 10 to 15 cc. of blood and is apparently independent of the peripheral systolic blood pressure and of the cardiac and respiratory rates. It is possible that this phenomenon may depend on variations in the activity of the vagus nerve, but there is no proof of this. Control

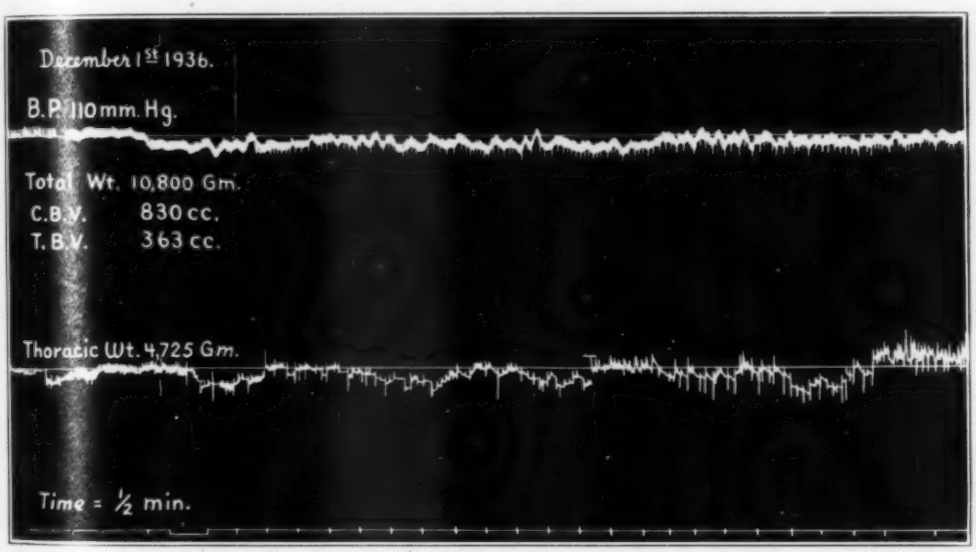

Chart 1.—Rhythmic variations in the amount of blood in the thorax (normal animal).

experiments were undertaken to determine what effect, if any, the anesthetic had on the regional redistribution of blood. It was found that pentobarbital sodium produces a centripetal flow of blood which is apparent as an increase of blood in the splanchnic and thoracic regions (fig. 2).

REGIONAL REDISTRIBUTION OF BLOOD AFTER HEMORRHAGE

This phase of the investigation was designed to determine the effect of graded hemorrhage and of hemorrhagic shock on the distribution of blood. The criterion of shock was a systolic blood pressure of 60 mm. of mercury (or less) which showed no spontaneous tendency to rise.

Head Area.—Hemorrhage results in a distinct loss of blood from this region (table 1; fig. 3 *A*). The decrease in weight occurs early, and a maximal loss is soon reached. In these experiments the decrement did not exceed 30 to 50 Gm. After the shock level of blood pressure is reached the loss of weight takes place more slowly and to a lesser extent. In the absence of direct observation of the pial vessels during this period of decrease in the blood pressure it is not possible to state that the loss of blood occurs from the brain. On the contrary, it has been shown (Fog [19]) that, while the pial vessels reveal an initial constriction, this is soon followed by dilatation when a fall of blood pressure is induced by

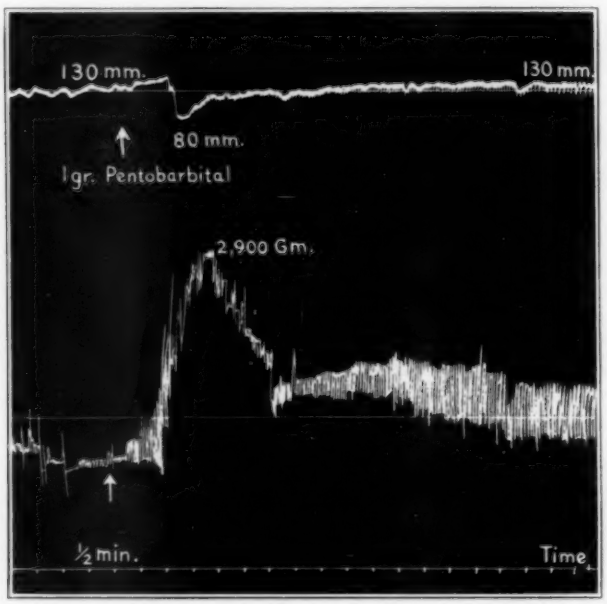

Chart 2.—Influence of pentobarbital sodium on the regional distribution of blood in the splanchnic region.

hemorrhage. The vasodilator impulses to the pial vessels may be mediated through the vagi (Cobb and Finesinger [20]).

Thoracic Area.—In the early stages of hemorrhage a flow of blood takes place into this region, as indicated by a transitory increase in weight (fig. 3 *B*). As the loss of blood continues, a decrease in weight follows which is dependent on the extent of the hemorrhage. The

19. Fog, M.: Cerebral Circulation: The Reaction of the Pial Arteries to a Fall in Blood Pressure, Arch. Neurol. & Psychiat. **37**:351 (Feb.) 1937.

20. Cobb, S., and Finesinger, J. E.: Cerebral Circulation: XIX. The Vagal Pathway of the Vasodilator Impulses, Arch. Neurol. & Psychiat. **28**:1243 (Dec.) 1932.

diminution of blood in this area frequently totals 100 to 200 cc. (table 2; fig. 3 *B*). The paradoxic shift of blood into the thorax during the early stages of hemorrhage may be explained by an overcompensating splanchnic vasoconstriction and possibly by an increase in the rate and amplitude of the respiratory movements. In these experiments hemorrhage was continued until shock was definitely present, but at no time was there evidence of vasomotor paralysis in the thoracic area. Active vasoconstriction was observed up to the moment of death (table 2).

TABLE 1.—*Influence of Hemorrhage on the Distribution of Blood in the Head Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Blood Withdrawn, Cc.	Blood Pressure, Mm. Hg	Weight of Head Area, Gm.	Time, Minutes
8.400	756	...	110	1,550	0
		100	80	1,527	
			90	1,527	
		200	60	1,509	
			30	1,509	
			25	1,509	60
			20	1,509	
			25	1,500	
			25	1,500	80

TABLE 2.—*Influence of Hemorrhage on the Distribution of Blood in the Thoracic Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Blood Withdrawn, Cc.	Blood Pressure Mm. Hg	Weight of Thoracic Area, Gm.	Time, Minutes
10,800	972	...	120	4,770	0
		120	110	4,845	
		130	90	4,995	
			90	4,745	
		125	90	4,645	60
			90	4,595	
			85	4,545	
		165	35	4,545	
			30	4,545	
			45	4,520	120

Splanchnic Area.—In this region hemorrhage causes excessive vasoconstriction, so that a large proportion of the blood removed appears to come from the splanchnic area. The loss of weight is greater than can be accounted for by the quantity of blood which has been withdrawn. This would appear to indicate an overcompensating vasoconstriction (table 3; fig. 3 *C*). That the loss of weight is due to active vasoconstriction and not merely to passive removal of blood is indicated by the continued active loss of weight in the splanchnic area in the interval between periods of hemorrhage. Splanchnic vasoconstriction, which is present from the onset of hemorrhage, becomes relatively greater after the shock level of blood pressure is reached and persists until death. In

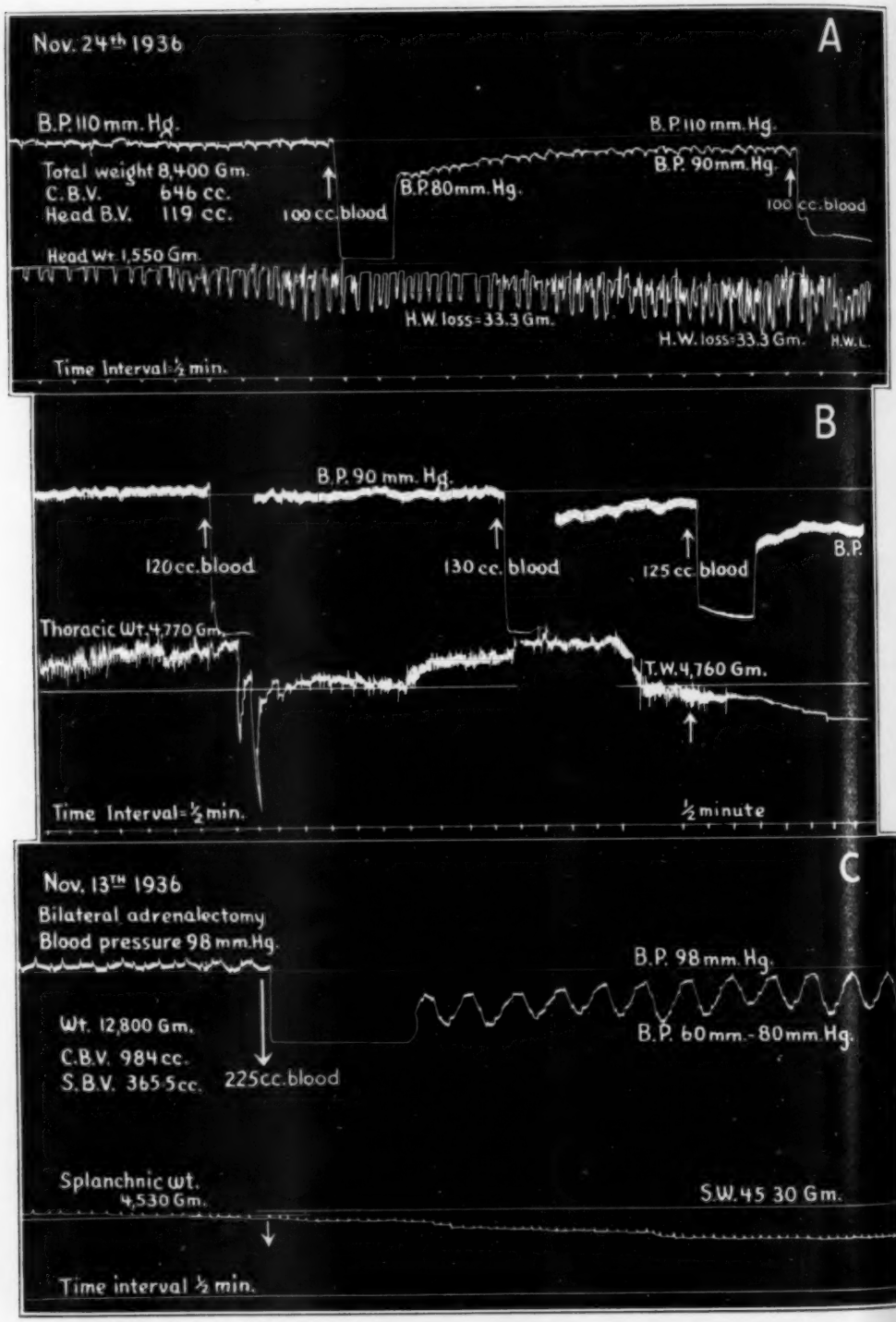

Chart 3.—*A*, influence of hemorrhage on the regional distribution of blood in the head region. *B*, influence of hemorrhage on the regional distribution of blood in the thoracic region. *C*, influence of hemorrhage on the regional distribution of blood in the splanchnic region.

order to determine to what extent the adrenal glands are a factor in the production of splanchnic vasoconstriction after loss of blood, bilateral adrenalectomies were performed. It will be noted (fig. 3 *C*) that vasoconstriction still occurs in the adrenalectomized animal after hemorrhage. These findings are not consistent with the presence of vasomotor paralysis in the splanchnic area in hemorrhagic shock. However, they do suggest that splanchnic vasoconstriction is dependent not on the presence of the adrenal glands but rather on the integrity of the sympathetic nervous system.

Peripheral Area.—The peripheral redistribution of blood after hemorrhage was studied. In the early stages of hemorrhage, when the blood pressure is still above shock level, a loss of weight takes place from

TABLE 3.—*Influence of Hemorrhage on the Distribution of Blood in the Splanchnic Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Blood Withdrawn, Cc.	Blood Pressure, Mm. Hg	Weight of Splanchnic Area, Gm.	Time, Minutes
8,450	760	...	100	5,535	0
		120	60	5,460	
			55	5,450	
			50	5,435	
			48	5,435	
		115	45	5,435	
			40	5,435	60
			40	5,435	
		60	25	5,260	
			15	5,210	
			10	5,185	
			10	5,160	
			10	5,110	
			8	5,160	
			8	5,085	120

the peripheral region. This suggests the presence of active vasoconstriction which is known to occur in the blood vessels of the skin. This shift of blood amounts to from 20 to 30 cc. If more blood is withdrawn and the blood pressure is brought to the shock level (60 mm. of mercury), the peripheral area regains its initial weight. If additional blood is removed and the blood pressure is lowered to the critical level (20 mm. of mercury), a gradual increase of weight occurs in the peripheral region, which amounts to the equivalent of 25 to 30 cc. of blood (table 4). The later translocation of blood into the periphery may be due to one or more of the following factors:

1. Peripheral vasomotor paralysis (Smith [12]).
2. Excessive peripheral vasoconstriction with a loss of plasma through the capillary walls (Malcolm [9]).
3. Vasoconstriction of the cutaneous blood vessels and vasodilatation of the blood vessels of the muscles (Starling [8]).

The work of various investigators (Seelig and Lyon [11]) indicates that peripheral vasoconstriction rather than peripheral vasomotor paralysis occurs in shock. In support of this it has been shown that the vasomotor reflexes can be elicited even in the presence of advanced secondary shock (Porter and Quimby; [21] Porter, Marks and Swift [22]). Evidence will be presented later in this paper to support the view that the late increase of weight in the periphery results from dilatation of the muscle capillaries and that it corresponds to the type of vascular redistribution produced by the administration of small amounts of epinephrine.

Résumé.—The regional redistribution of blood in the presence of hemorrhagic shock may be briefly recapitulated at this time. A shift of blood away from the head region always occurs. In the thoracic area there is an early increase in weight, probably as a result of excessive

TABLE 4.—*Influence of Hemorrhage on the Distribution of Blood in the Peripheral Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Blood Withdrawn, Cc.	Blood Pressure, Mm. Hg	Weight of Peripheral Area, Gm.	Time, Minutes
7,600	684	..	105	2,760	0
		50	100	2,754	
		50	100	2,747	
		70	60	2,740	
			80	2,773	
			50	2,760	
			55	2,773	60
			60	2,773	
		30	50	2,773	
		30	45	2,780	
			55	2,780	
			45	2,780	
			25	2,786	120

splanchnic vasoconstriction forcing blood into the thorax. Later the weight of the thoracic area decreases. The splanchnic area always shows a decrease in weight, and a large proportion of the blood lost by hemorrhage comes from this region. In a number of the animals in the present series of experiments the splanchnic vasoconstriction was excessive, so that the loss of weight which occurred in the splanchnic region was almost as great as the amount of blood lost by hemorrhage (table 3). Such animals, which may be termed hyperreactors, usually experienced shock more rapidly than did those animals in which excessive splanchnic vasoconstriction was not present. The peripheral region revealed an early loss of weight and then a gradual return to the initial weight level.

21. Porter, W. T., and Quimby, W. C.: Further Data Regarding the Condition of the Vasomotor Neurons in "Shock," Am. J. Physiol. **20**:500, 1908.

22. Porter, W. T.; Marks, H. K., and Swift, J. B.: The Relation of Afferent Impulses to Fatigue of the Vasomotor Centre, Am. J. Physiol. **20**:444, 1904.

In the later stages of hemorrhagic shock an increase of weight occurred, indicating a peripheral "pooling" of blood or blood plasma. The data presented suggest that peripheral vasoconstriction reaches its maximum in an early stage of shock, in contradistinction to splanchnic vasoconstriction, which is progressive up to the time of death.

A comparison was made of the regional changes in weight following hemorrhage. Representative data are shown in table 5, and it will be noted that the lowest percentage loss of weight was obtained in the peripheral area, where a loss of only 0.72 per cent is recorded. The percentage weight loss from the head area was low, being only 3.2 per cent. The dilatation of the cerebral blood vessels (Fog [19]) during hemorrhage was a factor in maintaining blood flow to the brain under the adverse conditions of hemorrhage. The greatest percentage losses of weight took place from the thoracic region and particularly from the splanchnic region, where as much as an 8.1 per cent loss of weight occurred.

TABLE 5.—*Relative Regional Change in Weight Following Hemorrhage*

Region	Weight, Gm.	Weight Loss, Gm.	Weight Loss in Percentage of Regional Weight
Head	1,550	50	3.2
Thorax	4,770	250	5.2
Splanchnic	5,535	450	8.1
Periphery (hindlimbs)	2,760	20	0.72

REGIONAL REDISTRIBUTION OF BLOOD AFTER TRAUMA

In this phase of the study the distribution of blood after trauma was investigated and compared with that after hemorrhage. Traumatic shock was produced by repeated blows to one or both hindlimbs with a padded hammer. Measurements of the regional weight were made prior to the trauma and also during the period of falling of the blood pressure. Care was taken not to break the continuity of the cutaneous surface.

The shift of weight in all areas was somewhat slower than that resulting from hemorrhagic shock. The head region showed a gradual loss of weight which did not exceed 30 to 50 Gm. In the early stages of traumatic shock there occurred an increase of weight in the thorax, but as shock deepened a gradual loss of weight took place (table 6). The total weight loss in all areas examined is obviously dependent on the size and weight of the individual animal. In the splanchnic region there is a progressive loss of weight which continues until death. It is rapid in the earlier phases of shock but becomes slower after the blood pres-

sure has fallen below the shock level. In many of these experiments a loss of weight equivalent to 30 to 40 per cent of the calculated blood volume was present (table 7). These findings suggest that a large proportion of the blood which escapes into the area of trauma is lost from the splanchnic region. The rate of fluid loss into the traumatized

TABLE 6.—*Influence of Trauma on the Distribution of Blood in the Thoracic Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Trauma	Blood Pressure, Mm. Hg	Thoracic Weight, Gm.	Time, Minutes
14,500	1,305	.....	125	3,900	0
		Trauma	115	4,020	
		Trauma	100	3,975	30
		Trauma	94	3,910	
		Trauma	90	3,880	
		Trauma	85	3,830	60
		Trauma	83	3,800	
			72	3,800	
			60	3,780	
			55	3,775	
			50	3,760	120
			50	3,770	
			45	3,750	
			30	3,735	
			30	3,735	180
			35	3,720	

TABLE 7.—*Influence of Trauma on the Distribution of Blood in the Splanchnic Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Trauma	Blood Pressure, Mm. Hg	Splanchnic Weight, Gm.	Time, Minutes
13,000	1,170	.....	110	5.500	0
		Trauma	100	5,475	
		Trauma	95	5,400	30
		Trauma	80	5,400	
		Trauma	90	5,350	60
		Trauma	70	5,375	
			63	5,350	
			50	5,325	
			45	5,300	
			50	5,275	120
			45	5,250	
			30	5,200	
			30	5,200	
			50	5,150	
			47	5,150	180

limbs was largely dependent on the extent and rapidity with which splanchnic vasoconstriction occurred. An increase in weight of the hind-limbs invariably occurred after trauma (table 8). Are we correct in assuming that this increase in weight, which may amount to the equivalent of 50 per cent of the calculated blood volume, is due to the accumulation of blood and blood plasma in the extravascular spaces of

the traumatized tissues? In view of the work of Lewis [23] on the local release of histamine from the skin, it would seem to be more reasonable to regard the increase in weight as being the result of two factors: (1) extravasation of blood and plasma into the extravascular spaces, and (2) dilatation of blood vessels in the area of trauma, particularly in the muscles, with a resulting segregation of blood within these vessels. A third factor, also, may be the imbibition of fluid by traumatized and dying cells. The regional redistribution of blood resulting from trauma was found to be similar to that following hemorrhage.

REGIONAL REDISTRIBUTION OF BLOOD AFTER ADMINISTRATION OF HISTAMINE

An investigation of the distribution of blood after the administration of histamine was undertaken in order to determine whether or not the

TABLE 8.—*Influence of Trauma of the Distribution of Blood in the Peripheral Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Trauma	Blood Pressure, Mm. Hg	Weight of Hindlimbs, Gm.	Time, Minutes
7,900	711	.....	115	2,000	0
		Trauma			
			95		
		Trauma	90		
		Trauma	70		
		Trauma	65		
		Trauma	50	2,320	60
				2,340	
				2,360	
			35	2,400	120
			30	2,435	
			30	2,450	180

activity of histamine-like substances could explain the phenomena of secondary shock. The existence of such toxic substances in secondary shock has been claimed (Cannon and Bayliss; [24] Dale and Richards; [25] Grunke and Haring [26]) and just as vigorously denied (Simonart; [27]

23. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

24. Cannon, W. B., and Bayliss, W. M.: Reports of the Special Investigation Committee on Surgical Shock and Allied Conditions: VIII. Traumatic Toxaemia as a Factor in Shock, Medical Research Committee, Special Report Series, no. 26, London, His Majesty's Stationery Office, 1919, p. 19.

25. Dale, H. H., and Richards, A. N.: A Vasodilator Action of Histamin and Some Other Substances, J. Physiol. **52**:110, 1918.

26. Grunke, W., and Haring, W.: Das Verhalten der Blutmenge beim experimentellen Shock, Ztschr. f. d. ges. exper. Med. **79**:763, 1931.

27. Simonart, A.: Etude expérimentale sur la toxémie traumatique et la toxémie des grands brulés, Arch. internat. de pharmacodyn. et de thérap. **37**:269, 1930.

Blalock;[28] Roome and Wilson;[29] O'Shaughnessy and Slome;[30] Smith;[12] Schneider;[31] Herbst[32]).

Histamine was injected intravenously in amounts of 0.00005 to 0.0002 mg., and the regional shift of blood was studied. In the head area there occurs a loss of weight with administration of varying quantities of histamine (table 9). It has been pointed out that histamine dilates the cerebral arterioles and causes an increased flow of blood through the brain (Forbes, Wolff and Cobb;[33] Weiss and Lennox[34]). On this basis, the shift of blood observed in the present studies must occur from the skin, muscles or bone of the head region.

In these experiments histamine induced a striking shift of blood into the thoracic region, as was evidenced by the rapid increase of weight. This translocation of blood persisted for long periods (one to three hours) and was present even after the systolic blood pressure had returned to the initial level (table 10; fig. 4 *A*). It was coincident with

TABLE 9.—*Influence of Histamine on the Redistribution of Blood in the Head Area*

Injection		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.0001 mg. histamine	Blood pressure, mm. Hg	105	45	75	100	100	100
	Weight of head, Gm.....	2,662	—28*	—22	—17	—10	—5
0.0002 mg. histamine	Blood pressure, mm. Hg	115	45	100	110	110	115
	Weight of head, Gm.....	2,630	—25	—8	—8	0	0

* Minus sign indicates loss.

the fall in systolic blood pressure. Considerable disagreement exists regarding the effect of histamine on the pulmonary circulation. A fall in

28. Blalock, A.: Experimental Shock: The Probable Cause for the Reduction in Blood Pressure Following Mild Trauma to an Extremity, Arch. Surg. **22**:598 (April) 1931.

29. Roome, N. W., and Wilson, H.: Experimental Shock: Effects of Extracts from Traumatized Limbs on Blood Pressure, Arch. Surg. **31**:361 (Sept.) 1935.

30. O'Shaughnessy, L., and Slome, D.: Etiology of Traumatic Shock, Brit. J. Surg. **22**:589, 1935.

31. Schneider, H.: Ueber das Vorkommen und über die Bedeutung von Gewebsgiften bei Shockzustanden des Menschen, Deutsche Ztschr. f. Chir. **229**: 343, 1930.

32. Herbst, R.: Experimentelles zur Entstehung des traumatischen Shocks, Arch. f. klin. Chir. **176**:98, 1933.

33. Forbes, H. S.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: X. The Action of Histamine, Am. J. Physiol. **89**:266, 1929.

34. Weiss, S., and Lennox, W. G.: The Cerebral Circulation: XVII. Cerebral Blood Flow and the Vasomotor Response of the Minute Vessels of the Human Brain to Histamine, Arch. Neurol. & Psychiat. **26**:737 (Oct.) 1931.

pressure in the pulmonary artery has been observed (David and Siedek [4]), while others have found that histamine increases the pulmonary arterial pressure (Hochrein and Keller [3]). It has been demonstrated that histamine, acting mainly on the pulmonary arterioles, constricts both the inflow and the outflow of the lungs (Inchley [35]). This observation has been confirmed by Gaddum and Holtz.[36]

Histamine in small doses produced a temporary shift of blood into the splanchnic region, followed by a decrease in the amount of blood in that area (table 11; fig. 4 *B*). The increase of splanchnic blood may be explained by temporary constriction of the hepatic veins with retardation of blood flow through the portal vessels (Mautner and Pick; [37] Bauer, Dale, Poulsson and Richards [38]). It is apparent that histamine is much

TABLE 10.—*Influence of Histamine on the Redistribution of Blood in the Thoracic Area*

Injection		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.0001 mg. histamine	Blood pressure, mm. Hg	110	40	90	110	110	110
	Thoracic weight, Gm.....	5,330	+233*	+200	+166	+100	+100

* Plus sign indicates increase.

TABLE 11.—*Influence of Histamine on the Redistribution of Blood in the Splanchnic Area*

Injection		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.0002 mg. histamine	Blood pressure, mm. Hg	100	40	100	100	100	100
	Splanchnic weight, Gm...	2,500	+150*	—50	—50	—25	—25

* Plus sign indicates increase; minus sign, loss.

more effective in altering the thoracic redistribution of blood than the splanchnic. These findings explain the observation that total splanchnic evisceration does not prevent the fall in blood pressure produced by histamine (Gotsev; Lueken and Simmendinger [39]).

35. Inchley, O.: Histamine Shock, J. Physiol. **61**:282, 1926.

36. Gaddum, J. H., and Holtz, P.: The Localization of the Action of Drugs on the Pulmonary Vessels of Dogs and Cats, J. Physiol. **77**:139, 1932.

37. Mautner, H., and Pick, E. P.: Ueber die durch Shockgifte erzeugten Zirkulationsveränderungen, Arch. f. exper. Path. u. Pharmakol. **142**:271, 1929.

38. Bauer, W.; Dale, H. H.; Poulsson, L. T., and Richards, D. W.: The Control of Circulation Through the Liver, J. Physiol. **74**:343, 1932.

39. Gotsev, T.; Lueken, B., and Simmendinger, W.: Ueber den Einfluss des Splanchnicusgebiets auf den allgemeinen Blutdruck, Ztschr. f. d. ges. exper. Med. **100**:81, 1936.

The peripheral distribution of blood is also affected by histamine. With small amounts (0.00005 mg.) there is a loss of blood followed by an increase in weight and finally a return to the initial level (table 12; fig. 5 *A*). With a larger dose (0.0001 to 0.0002 mg.) there is a definite shift of blood into the periphery (table 12; fig. 5 *B*).

It is evident that the redistribution of blood produced by administration of histamine differs from that produced by trauma or by hemor-

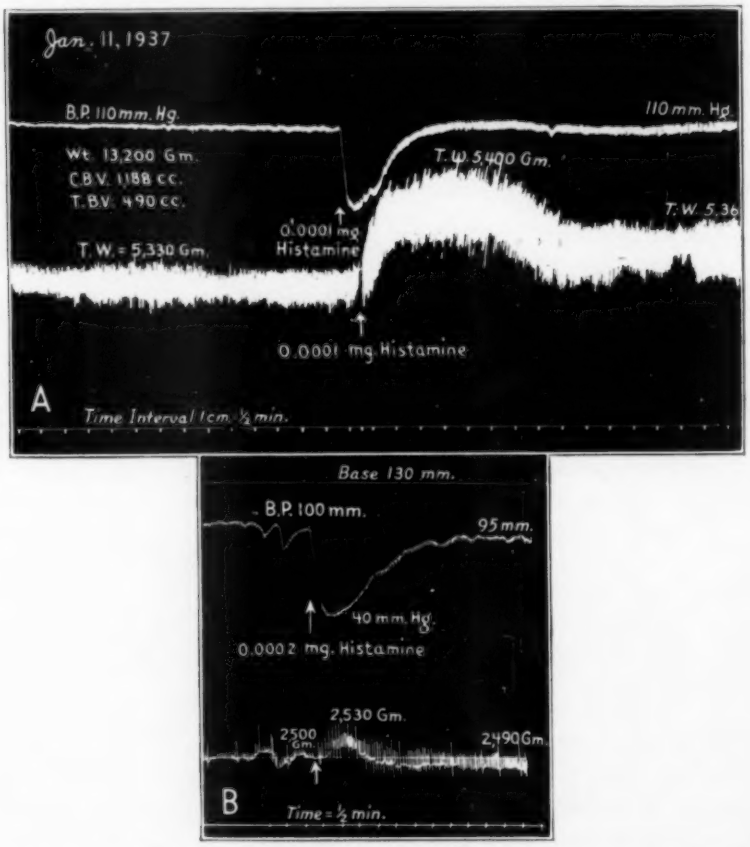

Chart 4.—*A*, influence of histamine (0.0001 mg.) on the regional distribution of blood in the thoracic region. *B*, influence of histamine (0.0002 mg.) on the regional distribution of blood in the splanchnic region.

rhage. Division of the spinal cord does not prevent the fall in blood pressure following administration of histamine. This indicates that the site of action is in the blood vessels (Hermann and Morin [40]).

40. Hermann, H. H., and Morin, G.: Démonstration cruciale chez le chien de l'origine périphérique du collapsus vasculaire dans différents états de choc, J. de physiol. et de path. gén. **33**:833, 1935.

REGIONAL REDISTRIBUTION OF BLOOD AFTER ADMINISTRATION OF EPINEPHRINE

Following the observation that the administration of large quantities of epinephrine results in a condition of shock accompanied by low blood pressure, diminished blood volume and concentration of the red blood cells, it was suggested that hyperactivity of the adrenal glands might be an etiologic factor in secondary shock (Bainbridge and Trevan;[41] Erlanger and Gasser[10]). Recently, considerable emphasis has been placed upon excessive activity of the adrenal glands as a factor in shock (Freeman[42]). For this reason a study has been made of the redistribution of blood after the administration of epinephrine. Epinephrine hydrochloride was injected intravenously in varying amounts from 0.02 to 3 mg.

After the injection of epinephrine there occurred a distinct shift of blood from the head region, as is shown by the rapid loss of weight

TABLE 12.—*Influence of Histamine on the Redistribution of Blood in the Peripheral Area*

Injection		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.00005 mg. histamine	Blood pressure, mm. Hg.	115	40	105	115	115	115
	Peripheral weight, Gm...	3,570	−50*	−25	0	0	0
0.0001 mg. histamine	Blood pressure, mm. Hg.	95	25	75	75	95	95
	Peripheral weight, Gm...	3,570	+50*	+30	+10	0	0

* Minus sign indicates loss and plus sign increase.

(table 13; fig. 6*A*). This was present both with small and with large doses. That the brain itself may partake of this shift of blood is possible, in view of definite proof of the existence of a vasomotor innervation of the cerebral vessels (Forbes et al;[33] Westenrijk[43]). Moreover, epinephrine has been shown to exert a constricting effect on the blood vessels of the isolated canine brain (Wiggers[44]).

41. Bainbridge, F. A., and Trevan, J.: Surgical Shock and Some Allied Conditions, Brit. M. J. **1**:381, 1917.

42. Freeman, N. E.: Decrease in Blood Volume After Prolonged Hyperactivity of the Sympathetic Nervous System, Am. J. Physiol. **103**:185, 1933.

43. Westenrijk, N.: Untersuchungen über die Wechselbeziehungen der einzelnen Kreislaufgebiete: II. Ueber das vasomotorische Verhalten der Gehirngefässe, Ztschr. f. d. ges. exper. Med. **93**:1, 1934.

44. Wiggers, C. J.: Further Observations on the Constricting Action of Adrenaline on the Cerebral Vessels, J. Physiol. **48**:109, 1914.

In a dose of 0.02 mg. epinephrine causes a flow of blood into the thoracic region which, after several minutes, is followed by a return to the initial level and finally by a slight diminution of the blood in this area (table 14). Large amounts (2 to 3 mg.) produce a marked shift

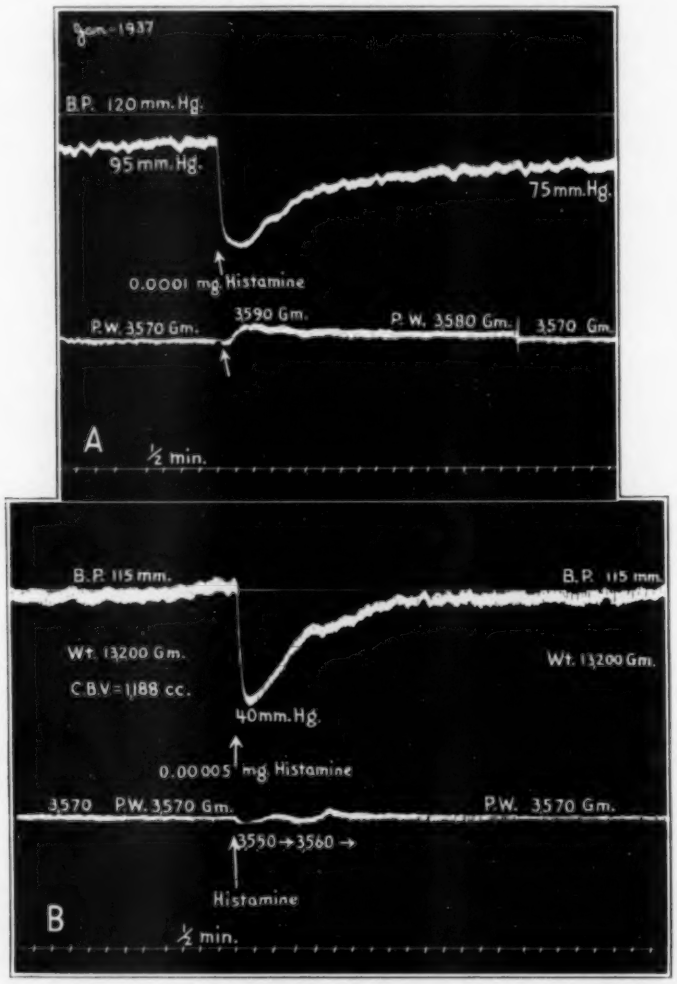

Chart 5.—*A*, influence of histamine (0.0001 mg.) on the regional distribution of blood in the peripheral region. *B*, influence of histamine (0.00005 mg.) on the regional distribution of blood in the peripheral region.

of blood from the thoracic area and a loss of weight which is maintained for periods of one-half to one hour (table 14; fig. 6*B*). These results are in agreement with those of others, who have found that small amounts of epinephrine cause dilatation of the pulmonary blood vessels,

(Brodie and Dixon;[45] Langlois and Desbouis;[46] Führer and Starling;[47] Rothlin;[48] Anderes and Cloetta[49]), while large amounts produce pulmonary vasoconstriction (Tribe[50]).

The splanchnic region after the administration of a small amount of epinephrine (0.02 mg.) exhibits a definite and rapid loss of blood (table 15; fig. 7 *A*). This is followed after a variable period by a secondary shift of blood into the splanchnic area, this phase being accom-

TABLE 13.—*Influence of Epinephrine on the Redistribution of Blood in the Head Area*

Experiment 27		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.02 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	95	120	95	95	100	95
	Weight of head, Gm.....	2,675	—25*	—42	—25	—21	—15
Experiment 25							
2 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	110	180	150	100	70	100
	Weight of head, Gm.....	1,670	—26	—21	—20	—23	—18

* Minus sign indicates loss.

TABLE 14.—*Influence of Epinephrine on the Redistribution of Blood in the Thoracic Area*

Experiment 22		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.02 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	130	160	130	130	130	130
	Thoracic weight, Gm....	5,430	+50*	—16	—16	—16	—16
Experiment 23							
2 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	125	240	160	100	100	100
	Thoracic weight, Gm....	5,400	—100*	—130	—166	—200	—233

* Plus sign indicates increase and minus sign loss.

45. Brodie, T. G., and Dixon, W. E.: On the Innervation of the Pulmonary Blood Vessels and Some Observations on the Action of Suprarenal Extract, J. Physiol. **30**:476, 1904.

46. Langlois, S., and Desbouis, P.: Adrénaline et circulation pulmonaire, Compt. rend. Soc. de biol. **72**:674, 1912.

47. Führer, H., and Starling, E. H.: Experiments on the Pulmonary Circulation, J. Physiol. **47**:286, 1913.

48. Rothlin, E.: Experimentelle Untersuchungen über die Wirkungsweise einiger chemischer vasotonisierender Substanzen organischer Natur auf überlebende Gefässe, Biochem. Ztschr. **111**:257, 1920.

49. Anderes, E., and Cloetta, M.: Der Beweis für die Kontraktilität der Lungengefässe und die Beziehung zwischen Lungendurchblutung und O_2- Resorption, Arch. f. exper. Path. u. Pharmakol. **79**:301, 1915.

50. Tribe, E. M.: Vasomotor Nerves in the Lungs, J. Physiol. **48**:154, 1914.

panied by an increase in weight. With a larger dose of epinephrine (2 to 3 mg.) there occurs an early shift of blood from the region, which is of short duration and is soon followed by a secondary increase in the

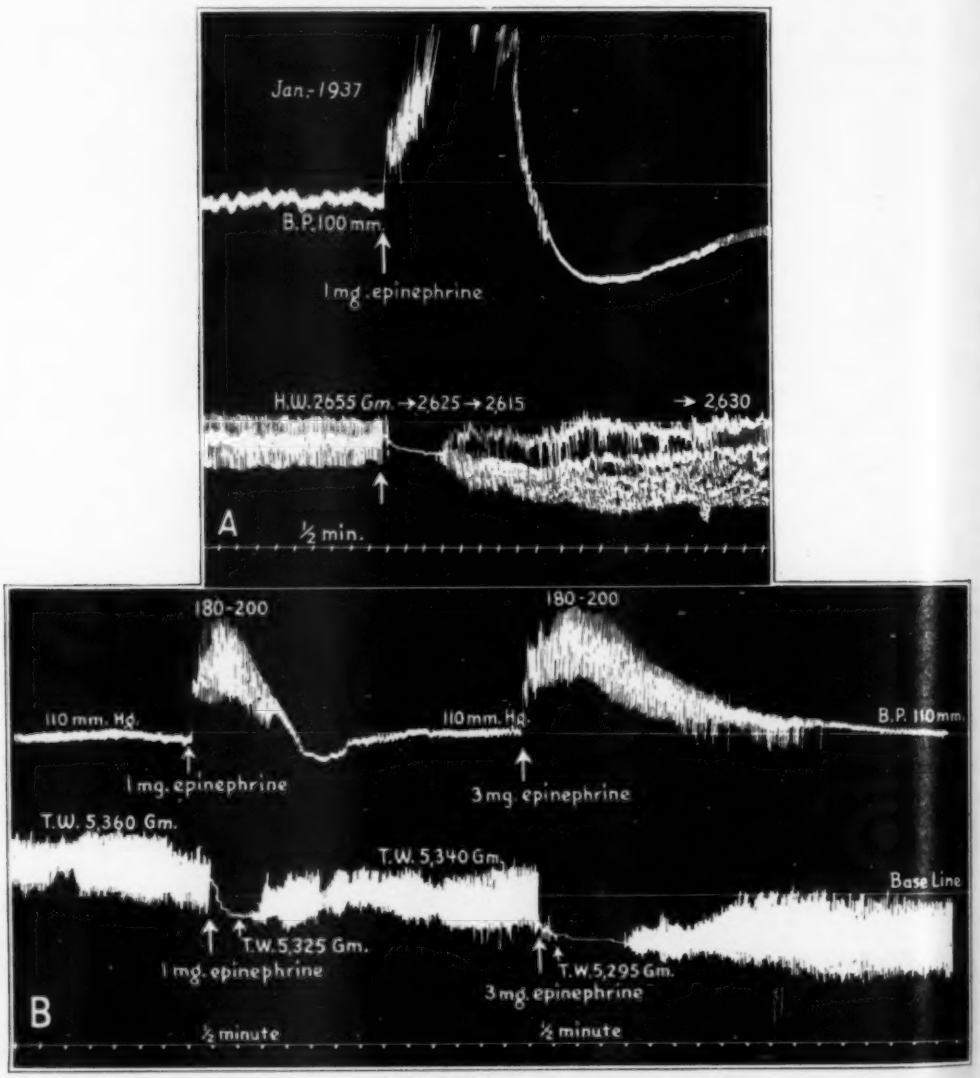

Chart 6.—*A*, influence of epinephrine (1 mg.) on the regional distribution of blood in the head region. *B*, influence of epinephrine (1 to 3 mg.) on the regional distribution of blood in the thoracic region.

amount of splanchnic blood. This increase persists for a longer period (table 15; fig. 7 *B*). The redistribution of blood is to some extent independent of the systolic blood pressure (table 15). It has been

observed that epinephrine in small amounts constricts and in large amounts dilates the blood vessels of the intestine (Hartman and McPhedran [51]). This vasodilatation has been shown to result from its action on the superior mesenteric ganglion and on the dorsal root ganglions of the lower portion of the thoracic region (Hartman, Kilborn and Fraser [52]).

It is well known that in certain of the viscera the effect of epinephrine is vasoconstrictor no matter how large or how small the dose

TABLE 15.—*Influence of Epinephrine on the Redistribution of Blood in the Splanchnic Area*

Experiment 14		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.02 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	130	170	130	130	130	130
	Splanchnic weight, Gm..	2,600	—225*	—225	—150	—25	+50
Experiment 16							
2 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	125	200	200	140	85	100
	Splanchnic weight, Gm..	2,555	—225*	—125	—75	+175	+175

* Plus sign indicates increase and minus sign loss.

TABLE 16.—*Influence of Epinephrine on the Redistribution of Blood in the Peripheral Area*

Experiment 7		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.02 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	130	160	95	130	130	130
	Peripheral weight, Gm..	3,500	+62*	+37	+25	+25	+15
Experiment 9							
1 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	115	270	140	65	100	100
	Peripheral weight, Gm..	3,570	+25	—25	—62	+12	+25

* Plus sign indicates increase and minus sign loss.

may be. Such viscera are the spleen (Hartman and McPhedran [51]) and the kidney (Hoskins and Gunning [53]).

In small quantities (0.02 mg.) epinephrine produces a translocation of blood into the peripheral area studied (table 16, fig. 8 *A*), which may

51. Hartman, F. A., and McPhedran, L.: Further Observations on the Differential Action of Adrenalin, Am. J. Physiol. **43**:311, 1917.

52. Hartman, F. A.; Kilborn, L. G., and Fraser L.: Adrenalin Vasodilator Mechanisms, Am. J. Physiol. **46**:502, 1918.

53. Hoskins, R. G., and Gunning, R. E. L.: The Effects of Adrenin on the Distribution of Blood: Volume Changes and Venous Discharge in the Kidney, Am. J. Physiol. **43**:304, 1917.

persist for periods up to one-half hour. In larger doses (1 to 2 mg.) the effect of epinephrine is triphasic. There is an initial increase in weight of the area, followed by a more prolonged decrease and finally a

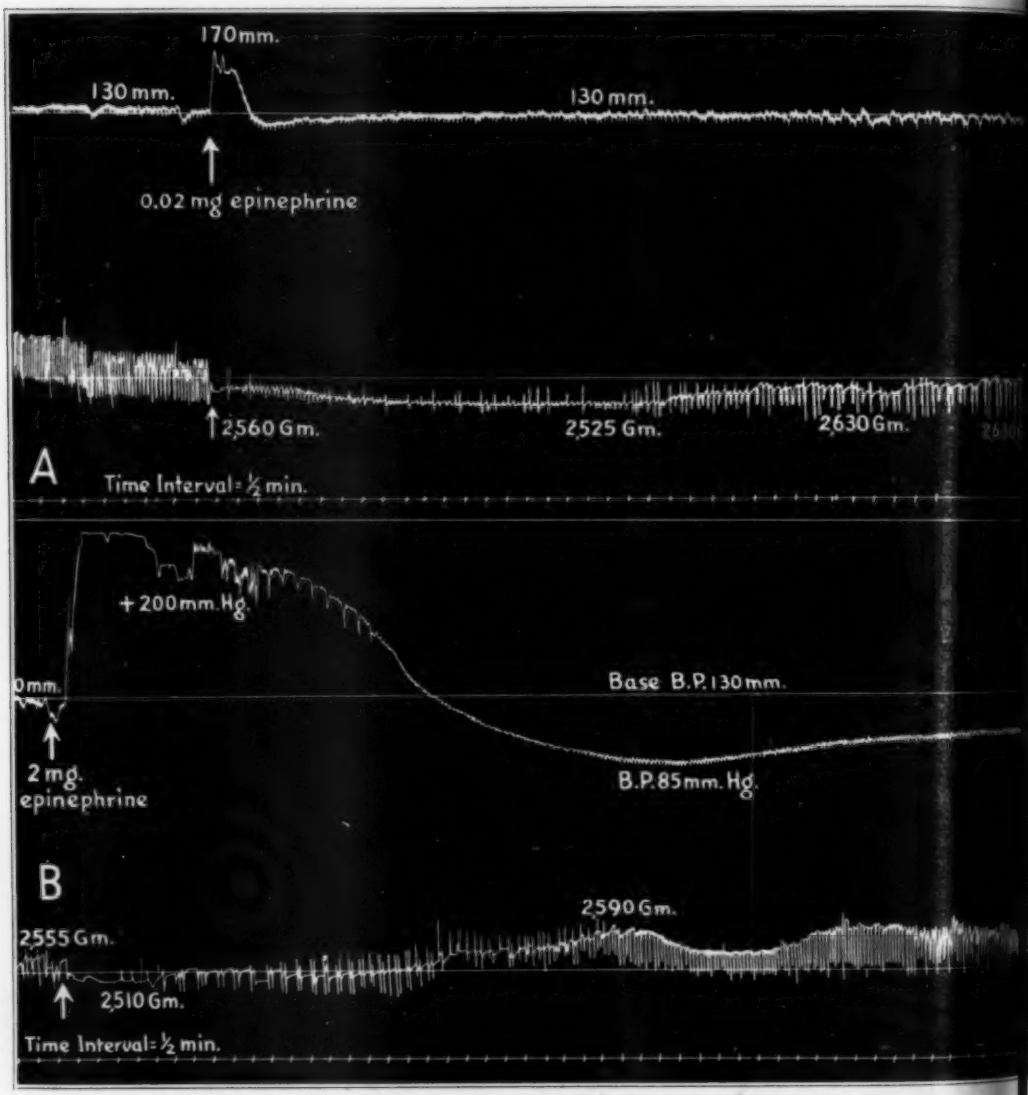

Chart 7.—*A*, influence of epinephrine (0.02 mg.) on the regional distribution of blood in the splanchnic region. *B*, influence of epinephrine (2 mg.) on the regional distribution of blood in the splanchnic region.

terminal slow increase (table 16; 8 *B*). Apparently, the predominant effect of epinephrine, both in small and in large amounts, is to produce a shift of blood into the periphery.

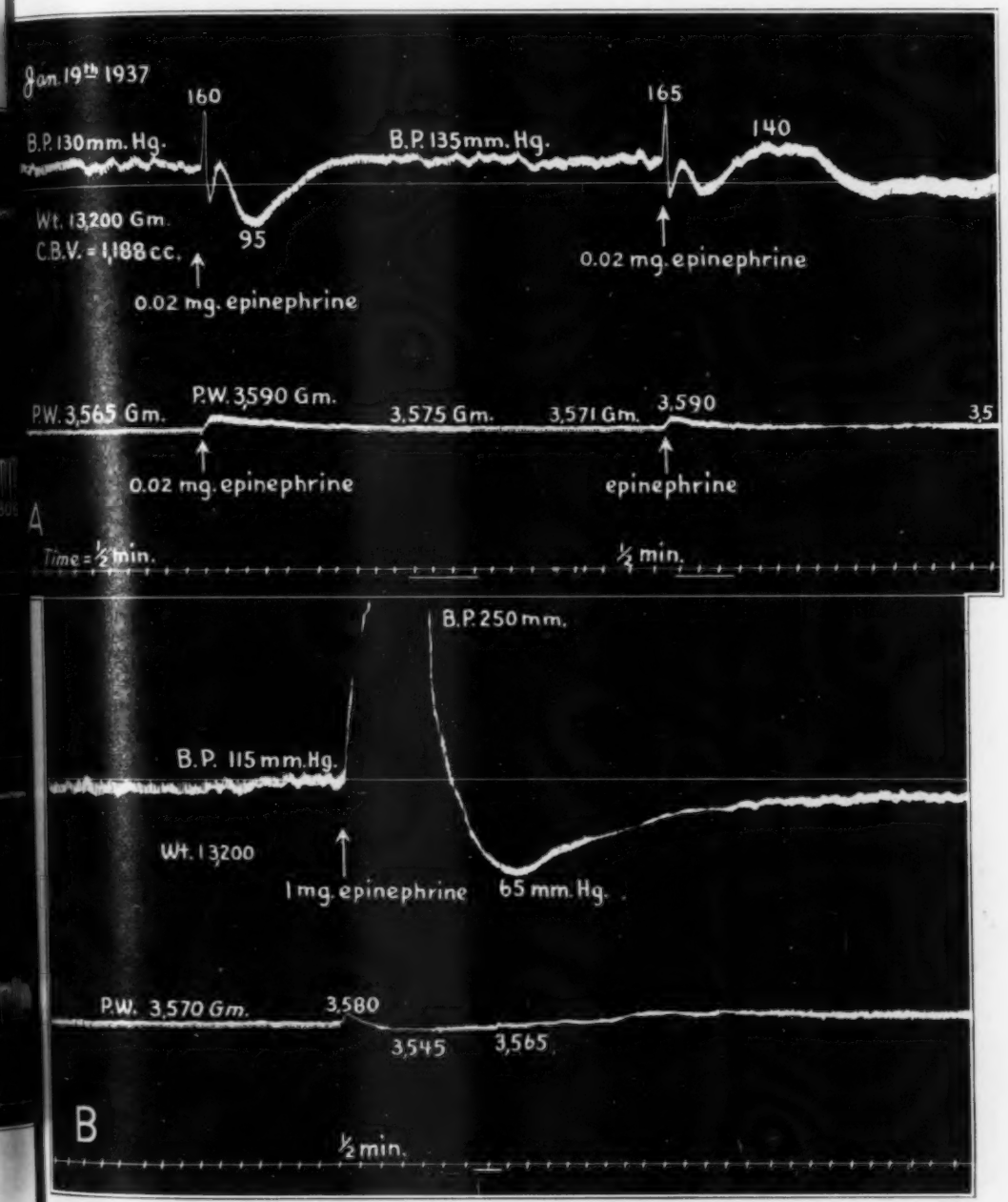

Chart 8.—*A*, influence of epinephrine (0.02 mg.) on the regional distribution of blood in the peripheral region. *B*, influence of epinephrine (1 mg.) on the regional distribution of blood in the peripheral region.

Epinephrine in large or small amounts will produce a constriction of the vessels of the skin (Hoskins, Gunning and Berry [54]). On the contrary, the blood vessels of the muscles are dilated by small amounts (Gunning; [55] Clark [56]) and constricted by large amounts (Gunning [55]). The site of action of epinephrine is believed to be mainly in the capillaries (Dale and Richards; [25] Clark [56]) and possibly also in the arterioles. Vasodilatation caused by epinephrine in the muscles of the hindlimbs results from the action of the substance on the sympathetic ganglions of the lower part of the lumbar and the sacral region and on the dorsal root ganglions of the nerves supplying the hindlimbs (Hartman, Kilborn and Fraser [52]).

COMMENT

This investigation has furnished proof of a striking similarity between the regional redistribution of blood after hemorrhage and that after trauma (Davis [57]). The noticeable feature in both is the excessive shift of blood from the splanchnic area, which seems to act as a reserve depot for blood. In both instances there occurs an early increase of blood in the thoracic area, followed by a decrease. Finally, in both evidence is presented which suggests a late dilatation of the peripheral blood vessels. The impression has been received from these experiments that this peripheral vasodilatation takes place chiefly in the muscles and is merely a passive vasodilatation in response to the excessive splanchnic vasoconstriction. The question is presented: Is this splanchnic vasoconstriction deleterious to the organism? When shock is the result of simple loss of blood the splanchnic vasoconstriction is beneficial and is apparently the chief means whereby the blood pressure is elevated. However, in traumatic shock there is at once established a point of excessive permeability in the vascular system at the site of trauma. Consequently, the effect of splanchnic vasoconstriction is to force more blood into the area of trauma and beyond vasomotor control. In this manner a vicious circle is established. Experiments may be cited to illustrate this point. It has been observed (O'Shaughnessy and Slome [30]) that the induction of spinal anesthesia prolongs the life of an animal in

54. Hoskins, R. G.; Gunning, R. E. L., and Berry, E. L.: The Effects of Adrenin on the Distribution of Blood: Volume Changes and Venous Discharge in the Limb, Am. J. Physiol. **41**:513, 1916.

55. Gunning, R. E. L.: The Effects of Adrenin on the Distribution of Blood: Effect of Massive Doses on the Outflow from Muscle, Am. J. Physiol. **43**:395, 1917.

56. Clark, G. A.: Adrenaline Vasodilatation in Voluntary Muscle, J. Physiol. **84**:344, 1935.

57. Davis, H. A.: Factors in the Production and Treatment of Shock: An Experimental Study, M. Ann. District of Columbia **6**:344, 1937.

a state of traumatic shock. This may be explained readily. Spinal anesthesia, by blocking vasoconstrictor impulses to the splanchnic area, prevents or diminishes the excessive splanchnic vasoconstriction and thus decreases the rate of fluid loss into the site of trauma. Trauma renders an animal sensitive to even a small hemorrhage. It has been demonstrated that the splanchnic vasoconstrictor mechanism becomes increasingly sensitive to each succeeding insult, so that when shock is established even a small hemorrhage may lead to an exaggerated splanchnic vasoconstriction (table 3). Such a "sensitization" takes place after trauma, and the addition of a small hemorrhage will induce, in the same manner, an excessive splanchnic outflow of blood into the site of trauma.

The redistribution of blood following administration of histamine does not resemble that following trauma or hemorrhage and therefore does not lend support to a toxic theory of secondary shock which is based on the release of histamine-like substances from the area of trauma (Cannon and Bayliss [24]). The influence of a small amount of epinephrine (0.02 mg.) on the distribution of blood is similar in many respects to that of hemorrhage and of trauma, i. e., it causes splanchnic vasoconstriction with a shift of blood into the thoracic and the peripheral region. The question arises: Is activity of the adrenal glands necessary for the production of this redistribution of blood? The answer is in the negative, as the same type of redistribution occurs in the adrenalectomized animal (fig. 3 *C*). The phenomena are dependent, apparently, on the activity of the sympathetic nervous system. An examination of representative data concerning peripheral vasoconstriction reveals that it becomes maximal soon after the reduction in blood pressure (table 4). Thereafter, efforts to maintain the blood pressure appear to depend on vasoconstriction in the splanchnic and thoracic areas.

SUMMARY AND CONCLUSIONS

A simple quantitative and qualitative method is described whereby regional translocations of blood in the intact animal can be recorded graphically. Results of the use of this method in a study of experimental secondary shock are given.

The redistribution of blood following hemorrhages is similar to that following trauma.

Excitation of the sympathetic nervous system with small amounts of epinephrine produces an analogous type of redistribution of blood.

Direct experimental evidence is offered against the occurrence of a splanchnic "pooling" of blood in traumatic and hemorrhagic shock.

The action of histamine on redistribution of blood does not resemble that of hemorrhage, trauma or epinephrine. Emphasis is placed on the

splanchnic vasoconstrictor response, and evidence is presented regarding the importance of exaggeration of this response in hastening the onset of shock after trauma.

Excessive vasoconstriction in the splanchnic and to a lesser extent in the thoracic region forces blood toward the peripheral areas and into any site of abnormal vascular permeability such as might be produced by trauma.

This splanchnic and thoracic vasoconstriction is the direct response to a reduction in blood volume, whether the loss of blood occurs by external hemorrhage or into an area of trauma.

REVIEW OF UROLOGIC SURGERY

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(Concluded from page 396)

PROSTATE GLAND

Hypertrophy.—Wildbolz [35] pointed out the indications for transurethral resection and for prostatectomy on the basis of 81 cases. He, like most European urologists, has reserved transurethral resection for cases in which there were only moderate changes at the vesical neck and for cases in which the risk of prostatectomy would be excessive. He has removed large, easily bleeding prostate glands by the perineal route.

His results with transurethral resection were gratifying. There were no deaths, and in most cases the patients were in the hospital only a short time. After transurethral resection, 54 patients could empty their bladders completely, while 11 had a sufficient amount of residual urine to make catheterization necessary.

Flocks [36] discussed healing after transurethral prostatic resection performed with the McCarthy resectoscope.

35. Wildbolz, H.: Die Erfolge der transurethralen, elektrischen Prostataresektion bei Prostatahypertrophie, Schweiz. med. Wchnschr. **68**:517-519 (April) 1938.

36. Flocks, R. H.: Local Repair Following Transurethral Prostatic Resection: Its Rôle in the Clinical Events Associated with This Operation, Tr. Southwest. Br., Am. Urol. A., 1937, pp. 26-50.

Destruction of tissue is not more than 3 to 4 mm. in extent and is even. There is no marked increase in evidences of infection below the level of the destroyed tissue.

Epithelization can be expected to be complete in three to four weeks after the operation. Because of this rapid epithelization, scarring is not a prominent feature of repair.

Two facts are of the utmost importance in the understanding of repair and healing after partial prostatectomy: 1. When part of the hyperplastic tissue is removed, dislocation and intraurethral bulging of hyperplastic masses of tissue are caused. 2. The enlarged portion of the prostate gland is supplied, in the main, by the urethral group of arteries, which enter at the prostatic-vesical junction and then course distally through the prostatic tissue. These form the anatomic basis for marked postoperative sloughing and the production of poorly healing masses of tissue bulging into the urethra. The microscopic, gross and cystourethrographic characteristics of these masses were described.

Thompson and Habein [37] reviewed the cases of 1,200 patients 70 years of age or older on whom 1,361 transurethral prostatic resections were performed at the Mayo Clinic. Forty-two per cent of the patients were more than 75 years of age. In order to evaluate the general condition and the cardiovascular-renal status in the entire group of cases, 300 records which were considered to be a fair sample of the whole group were taken at random and were reviewed carefully. It is difficult to express graphically the condition of the patients as far as operative risk is concerned. Approximately 56.6 per cent of the 300 patients whose records were reviewed were considered to constitute risks of grade 3 or 4 (4 is greatest) because of generalized arteriosclerosis, hypertension, coronary disease, myocardial damage or renal insufficiency. For a large number of these patients the risk of suprapubic cystostomy was considered prohibitive. Approximately 36 per cent of the group were considered to constitute risks of grade 2 because of the presence of senile changes, diabetes, past cerebral vascular accidents or hypertension. In only 7.3 per cent of the 300 cases was the classification of minimal surgical risk made. An analysis of renal function in the entire series of 1,200 cases revealed that in 504 (42 per cent) there was a considerable degree of renal damage. Of these 504 patients, 39 per cent had values for urea of from 41 to 100 mg. per hundred cubic centimeters of blood; 24 patients (2 per cent), of from 101 to 200 mg., and 12 patients (1 per cent), more

37. Thompson, G. J., and Habein, H. C.: Transurethral Prostatic Resection: Experience with One Thousand and Two Hundred Patients Seventy Years of Age or More, Proc. Staff Meet., Mayo Clin. **13**:305-311 (May 18) 1938.

than 200 mg. Only 16 (1.3 per cent) of the entire group of 1,200 patients were subjected to preliminary suprapubic cystostomy.

From a review of these cases it is apparent that age and poor general condition no longer prevent surgical relief of urinary obstruction. Comparison of the ages of the patients in any consecutive series of cases in which transurethral resection has been performed with the ages of the patients in any earlier series of cases in which prostatectomy was performed at the Mayo Clinic revealed that ten times as many men more than 75 years of age are now submitting to operation for relief from urinary obstruction as when suprapubic prostatectomy was the operation of choice.

Carcinoma of the prostate gland is found in about 20 per cent of cases. By transurethral resection the obstructing tissue can be removed, which permits the patient to void urine comfortably and normally for as long as five or six years. Recurrences of urinary obstruction sometimes necessitate subsequent operation, and up to the present time no patient has chosen suprapubic drainage in preference to a second transurethral resection.

Thompson and Habein [37] emphasized the importance of careful preoperative survey of the cardiovascular system. Recent coronary occlusion and myocardial infarction demand postponement of operation for two to three months except in cases of great emergency. Substernal pain on exertion, paroxysmal nocturnal dyspnea and recurrent attacks of pulmonary edema are cardinal signs of coronary sclerosis and serious myocardial damage. Old persons do not tolerate digitalis well, and its use is restricted until definite indications are present, such as congestive heart failure with auricular fibrillation and edema.

The first consideration in the treatment of renal insufficiency resulting from urinary obstruction is the establishment of adequate drainage. This is best accomplished by the use of an inlying urethral catheter. The second most important consideration is the administration of ample quantities of fluid, an average of 3,000 to 4,000 cc. daily; in exceptional cases as much as 7,000 cc. daily may be advisable. In the presence of normal values for blood chlorides, a 5 or 10 per cent solution of dextrose may be chosen. Excessive use of physiologic solution of sodium chloride may lead to increased renal damage or may result in edema. Study of the carbon dioxide–combining power of the blood aids in recognition of the acidosis which may accompany renal insufficiency. Under these conditions, marked improvement in renal function frequently follows administration of appropriate alkaline solutions.

Spinal anesthesia is usually the best type of anesthesia for the elderly patient with prostatic obstruction. Fifty milligrams of procaine hydrochloride injected into the third lumbar interspace generally is sufficient. It is important that the operation be of short duration.

Extreme loss of blood and shock may occur if it is prolonged more than forty-five minutes. Thompson prefers to perform the operation at two sittings rather than to prolong a single operation unduly and to run the risk of dire consequences. Fall in blood pressure should be prevented by appropriate measures, or, if it occurs, the pressure should be restored as soon as possible. In the majority of the 1,200 cases the Thompson resectoscope was employed. With this instrument, usually 2 Gm. of tissue can be removed in each minute of the operation. At the conclusion of the operation a hemostatic bag may be inserted. Thompson and Habein expressed the belief that it is important for the patient to be out of bed the day after prostatic resection if possible. This plan, they feel, prevents cardiovascular complications. Of this series of 1,200 patients, 70.4 per cent did not have a temperature higher than 100 F. at any time during postoperative convalescence. With careful preoperative preparation and postoperative care and with increased experience and refinements in surgical technic, the scope of transurethral prostatic resection has so broadened that few patients are denied surgical relief of urinary obstruction. The mortality rate among the 1,200 patients, all of whom were more than 70 years of age, was 1.6 per cent.

Thompson [38] reviewed a series of 100 consecutive cases in which prostatic resection was performed in 1937 and compared the details of management with those in a similar series of 205 cases, reviewed in 1932. During the time the series of 205 patients was accumulating in 1932, 37 additional patients underwent suprapubic prostatectomy; therefore, in 84.7 per cent of cases transurethral operation was performed, while in 15.3 per cent the prostate gland was removed by open operation. During the time when the 100 consecutive patients were being treated in 1937 no patient was advised to have any form of operation except transurethral resection. The patients operated on in 1937 were older, on an average, than those operated on in 1932. In 1932, when the technic of transurethral resection was relatively imperfect, suprapubic drainage was employed in 17.5 per cent of the 205 cases. In 1937 preliminary cystostomy was not performed at the Mayo Clinic in any of the 100 cases. In 4 cases, however, cystostomy had been performed elsewhere.

In 1937 preoperative drainage of the bladder by inlying urethral catheter was employed in only 17 per cent of cases, although intermittent catheterization frequently was employed until completion of a general medical examination, transurethral resection being performed

38. Thompson, G. J.: Clinical Data Concerning Prostatic Resection, J. Urol. **40**:121-128 (July) 1938.

at the same time. The decrease in complications and febrile reactions seemed to justify this practice.

If a patient has advanced uremia, it is usually best to employ an inlying catheter; however, one should aim to rid the patient of the catheter at the earliest possible moment. Transurethral prostatic resection gradually is becoming a more thorough operation than it was formerly, as is evidenced by the figures which show, in the series of 1932, that there were only 5 cases (2.4 per cent) in which 25 Gm. or more of tissue were removed, whereas in the series of 1937, 46 per cent of cases fell into this category.

Of the series of patients operated on in 1932 with the Braasch-Bumpus punch, 10.5 per cent required a second or a third operation, whereas in the series of 1937, in which operation was done with the Thompson resectoscope, 4 per cent of the patients needed a second resection and none required three operations.

Thompson discussed some of the important details of surgical technic. Thorough postoperative drainage of the bladder through the inlying catheter is considered of great importance. Thompson does not employ a hemostatic bag routinely. Careful observation and aseptic technic in the handling of catheters and in postoperative lavage of the bladder are of paramount importance. He does not advise the routine employment of urinary antiseptics during the early postoperative period.

In the 1932 series of patients, 43 per cent had a postoperative temperature of more than 101 F., whereas in 1937 this degree of febrile reaction occurred in only 9 per cent. Epididymitis occurred postoperatively in 8 per cent of the cases in 1932 and in only 1 per cent of the series of 1937. Bilateral partial vasectomy was performed in 16 per cent of the cases in 1937. The period of hospitalization in 1937 was definitely shorter than in 1932. There was no mortality in either series. During the years 1931 to 1936 inclusive, Thompson performed approximately 1,800 prostatic resections, with 12 deaths, a mortality of less than 1 per cent.

Walther and Willoughby [39] stated that prostatic hyperplasia can no longer be regarded as an independent entity; it is inseparably bound up with endocrine changes affecting the pituitary body and the testis.

In cases of early prostatism or in cases in which some serious physical disability accompanies any type of prostatic obstruction and surgical operation therefore seems inadvisable, the androgens should be given conscientious trial. The disadvantage of this mode of treatment is that, as with insulin, a maintenance dose must be continued; therefore, contact with the patient is necessary for an indefinite period, and massage usually is indicated.

39. Walther, H. W. E., and Willoughby, R. M.: Hormonal Treatment of Benign Prostatic Hyperplasia, J. Urol. **40**:135-144 (July) 1938.

Preparations of androsterone and of testosterone propionate for oral and intramuscular use are available.

Using these substances, Walther and Willoughby have treated 15 patients with benign prostatic hyperplasia during the past two years, with resulting clinical improvement.

Cancer.—Semans [40] reported a case of carcinoma of the prostate gland with metastasis in the testis.

The metastatic growth in the testis was too small to be felt on physical examination and was first found on microscopic examination of a routine section of the testis.

In many sections of the cord no trace of the tumor could be seen. The assumption is therefore that the cells came by way of the arteries leading to the testis. The tumor cells in the veins and lymphatic structures of the testis may have arisen from the tumor tissue lying among the seminiferous tubules.

Of the 140 cases of primary carcinoma of the prostate gland indexed in the files of the Johns Hopkins Hospital, the tumor involved by extension the pelvic lymph nodes in 43 cases, the bladder in 31, the seminal vesicles in 21 and the rectum in 8. Metastatic growths were found in the lungs in 26 cases; in the osseous system in 18; in the retroperitoneal, mediastinal and bronchial lymph nodes in 16; in the liver in 12; in the ureter in 7; in the pleura in 5; in the adrenal glands in 5; in the diaphragm in 4; in the peritoneum in 3, and in the pancreas in 2. The vas deferens, the urethra and the kidney were each involved in 1 instance.

URETHRA

Prolapse.—Berry and Greene [41] stated that prolapse of the urethra is an entity in the field of urology which, although uncommon, is most often seen in young girls.

Circular amputation of the prolapsed mucosa is a satisfactory form of treatment. Gynecologists who have used this method report no recurrence. Possible hemorrhage is adequately controlled by an inlying catheter.

The argument that stricture may result from the amputation is reduced in importance when the ease with which stricture can be prevented by timely postoperative dilation of the urethra is considered.

The simplicity of the circular amputation operation with the radio knife in itself has much to recommend its use in cases of prolapse of the mucous membrane of the urethra. Recognition of the fact that

40. Semans, J. H.: Carcinoma of the Prostate with Metastasis in the Testis, J. Urol. **40**:524-529 (Oct.) 1938.

41. Berry, N. E., and Greene, H.: Prolapse of the Female Urethra, J. Urol. **39**:92-96 (Feb.) 1938.

prolapse is chiefly due to redundancy of the mucosa and the fact that the operation is effective certainly justify its use.

Stone.—Stoccada [42] reported the case of a man aged 66 who had carried a gonococcic infection for more than forty years. There was a diverticulum behind a urethral stricture in which was pocketed a stone which had not caused symptoms. The stone weighed 155 Gm. and was composed mostly of phosphates.

GENITAL TRACT

Tuberculosis.—Menville and Priestley [43] reported their study of tuberculosis of the male genital tract in 62 cases in which postmortem examination had been performed. The average age of the patients at death was 43.9 years. Trauma and infection seemed of slight, if any, etiologic significance.

For practical purposes, tuberculous lesions in the genitalia should always be considered secondary to tuberculous foci elsewhere in the body (96.8 per cent). In this study, lesions elsewhere in the body were observed most often in the kidney (51.6 per cent) and less often in the lymph nodes, lungs and other organs. Miliary tuberculosis is frequently a terminal event in cases of genital tuberculosis in which death occurs. Lesions were found in the genitalia in the following order of frequency: prostate gland, epididymis, seminal vesicle and testis. If renal tuberculosis is present the prostate gland is almost always involved; this is not equally true of the epididymis. If renal tuberculosis is not present the epididymis is frequently involved, although the prostate gland may be normal. The route of infection and the actual pathologic relation of involvement in one part of the genital tract to involvement in another are in many cases difficult to determine.

Wells [44] contended that tuberculous epididymitis is always secondary to tuberculosis of the urinary tract and therefore that every patient who has tuberculous epididymitis should be suspected of having renal tuberculosis.

The path of invasion is as follows: from the blood stream to the kidney, from the kidney to the bladder by the urinary stream and from the posterior portion of the urethra to the epididymis by the lumen of the vas deferens. Wells based his conclusions (1) on clinical evidence in 55 cases, (2) on an analogy to pyogenic epididymitis and (3) on reasoned deductions from established facts.

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42. Stoccada, F.: Calcolo gigante dell'uretra posteriore, Schweiz. med. Wchnschr. **68**:859-860 (July 16) 1938.

43. Menville, J. G., and Priestley, J. T.: Tuberculosis of the Male Genital Tract: A Pathologic Study, J. Urol. **40**:66-73 (July) 1938.

44. Wells, C. A.: Tuberculous Epididymitis, Brit. J. Urol. **10**:114-130 (June) 1938.

Epididymectomy is the operation of choice for tuberculous epididymitis. Because of the frequency of subsequent infection of the opposite side, under certain circumstances the vas on the healthy side may be ligated and divided. This operation prevents contralateral involvement and should be done (*a*) when the patient is old, (*b*) when one testis has been completely destroyed or needlessly sacrificed and (*c*) in the presence of frank prostatitis and vesiculitis. In the absence of epididymitis vasoligation is reasonable when urinary tuberculosis is present.

Seminal Vesiculitis.—Peterson [45] stated that seminal catheterization is advocated as a practical, painless and nontraumatic procedure if properly done on a prepared patient.

On injection, the vesicle fills first, the ampulla next and the vas deferens last. The explanation of this phenomenon is to be found in the law that liquids flow in the direction of least resistance, which also explains why injection into the ampulla and vas deferens cannot be made if the catheter does not fit the ejaculatory duct, leaving the way open for the dye to regurgitate.

The presence of valves in the ampulla or the assumption that tonic closure of the ampulla takes place could not be substantiated.

Dilation of the ejaculatory ducts or injection of the seminal tract should be followed by ejaculation within two to three hours in order to promote drainage and prevent epididymal complications.

Vesiculograms made after injection of suitable contrast material reflect the size, shape and structure of the seminal vesicles as well as the relative topographic relation of the ampullae and the vasa deferentia.

Vesiculograms showing the characteristics of the normal vesicle and various types of pathologic vesicles obtained through retrograde catheterization were offered.

Improvement in the drainage and structure of the seminal vesicles, obtainable through retrograde catheterization of the ejaculatory ducts, was proved roentgenographically.

URINARY INFECTIONS

Helmholz [46] gave the essentials of diagnosis and treatment of infections of the urinary tract in infancy and childhood.

In the consideration of urinary antiseptics there is a wide choice, but in the last analysis two drugs stand out prominently above the rest, namely, mandelic acid and sulfanilamide. Sulfanilamide has a number

45. Peterson, A. P.: Retrograde Catheterization in Diagnosis and Treatment of Seminal Vesiculitis, J. Urol. **39**:662-677 (May) 1938.

46. Helmholz, H. F.: Urinary Infections in Infancy and Childhood: Diagnosis and Treatment, J. A. M. A. **111**:1719-1722 (Nov. 5) 1938.

of advantages over mandelic acid: It can be given in the acute stage of the infection; its bactericidal effect is not entirely dependent on the reaction of the urine, and it is excreted in bactericidal quantities by kidneys that are severely injured.

Administration of sulfanilamide does not offer any special difficulties. It is taken readily by infants and older children by mouth, and when it is not tolerated because of gastric irritability it can be given subcutaneously or intravenously. Its use in the acute stages of the infection, especially in infants, is a definite advance over the previous use of only diuresis and alkalization.

In infections caused by Proteus ammoniae the urine is strongly alkaline. In the treatment of this type of infection sulfanilamide is the drug of choice because of its superior action on alkaline urine and because of the difficulty in bringing the urine into the acid range necessary for the bactericidal action of mandelic acid or methenamine.

A particular advantage of sulfanilamide, which deserves emphasis, is the possible concentration that is bactericidal in the urine of patients who have injured the kidneys. It has been Helmholz' experience with the ketogenic diet and with methenamine and mandelic acid that an injured kidney cannot secrete a urine of low p_H, and even in cases in which the concentration of urea in the blood is normal the injured kidney cannot be beneficially influenced because of this difficulty. It is striking, therefore, that sulfanilamide can be excreted in the urine in sufficient concentration in cases in which the concentration of urea in the blood is well above normal.

Sulfanilamide is given in two-thirds the usual dose for streptococcic infections; that is, 10 grains (0.65 Gm.) per 20 pounds (9 Kg.) of body weight is given daily. From four to six doses are given daily. Sodium bicarbonate is given in doses of from 30 grains (2 Gm.) to 60 grains (4 Gm.) a day. Water usually is given in the usual amounts, but the intake of fluids can be restricted if the concentration of sulfanilamide in the urine remains low. A concentration of 50 mg. of the drug in its free form in 100 cc. of urine usually is secured from this dose. After the urine has become sterile it is essential to keep it so for four to six days and then to discontinue medication. After four days cultures are again made, to ascertain that the urine has remained sterile. In a number of cases concentrations of half this amount have brought about sterilization of the urine. When the drug has been administered in this manner it has only exceptionally given rise to cyanosis, and in Helmholz' experience it never has caused agranulocytosis or anemia.

The field of usefulness of mandelic acid has been narrowed considerably by the introduction of sulfanilamide, but the former drug still is useful, not only for streptococcic infections but because of its

effect on all bacteria, cocci and bacilli alike; when a proper concentration of the acid in the urine and a proper p_H of the urine are obtained it is a most dependable drug. As determined in vitro and therapeutically, it acts equally well in bacillary and in coccic infections.

Mandelic acid is administered as the elixir of ammonium mandelate or as ammonium mandelate in suppositories. It is given in doses that will produce a concentration of from 0.5 to 1 per cent of the drug in the urine. At the Mayo Clinic, Helmholz administers 1 Gm. for each 100 cc. of urinary output in the twenty-four hours. As most of the mandelate is excreted in the urine, a concentration of approximately 1 per cent results.

McMartin, Schmitz and McMartin [47] stated that most ambulatory patients cannot tolerate more than 20 to 40 grains (1.2 to 2.5 Gm.) of sulfanilamide daily. On account of the many severe phenomena that may follow its administration, such as variable grades of dermatitis and anemia, it should be dispensed on nonrefillable prescriptions. Old persons do not tolerate the drug as well as do young persons.

Sulfanilamide is not of much value in treatment of infections of the upper part of the urinary tract or of the bladder when drainage is insufficient or when calculi are present. The response of acute gonorrheal infections is best if patients have sought treatment at the first appearance of the discharge. Delay of a few days usually means a longer time before a sterile smear is obtained. The drug has been found to be specific against infections with Bacillus coli if drainage is sufficient and if calculi are not present.

All subjective symptoms caused by the drug disappear shortly after its administration has been stopped.

Cook [48] stated that mandelic acid is most efficacious under the following conditions: (1) when the urine is brought into direct and continued contact with the infected surface; (2) when the infection is largely superficial; (3) when there are no marked cicatricial changes in the renal tissues as a result of long-standing infection; and (4) when there is no obstruction to the drainage of urine. When the drug is administered in adequate doses (32 cc. of the syrup daily or 48 cc. of the elixir of mandelic acid daily) uncomplicated bacillary infections of the urinary tract will be cleared up in 90 per cent of cases. Occasionally two courses of treatment are necessary. Cocci, as a rule, are not affected by this form of therapy, with the exception of Streptococcus faecalis. When chronic prostatitis is associated with urinary

47. McMartin, C.; Schmitz, W. H., and McMartin, W. J.: Use of Sulfanilamide in Genito-Urinary Infections, J. Urol. **40**:233-238 (July) 1938.

48. Cook, E. N.: Chemotherapy in Infections of the Urinary Tract, J. Urol. **39**:692-698 (May) 1938.

infection the results with mandelic acid are not so good until the prostatitis has been eliminated.

When renal function is not good, mandelic acid must be administered with care. Nausea and (sometimes) vomiting are the most common complications following the use of mandelic acid. In 1 to 2 per cent of cases microscopic hematuria is noted, and occasionally gross hematuria may follow administration of this drug.

Recently sulfanilamide has been more widely used than before in treatment of infections of the urinary tract. The usual procedure is to give 60 grains (3.8 Gm.) each day for two or three days, then to reduce to 40 grains (2.5 Gm.) daily for the remainder of the treatment, which is continued generally for eight to fourteen days. This treatment may be repeated if necessary. For elderly patients the initial dose is 40 grains daily. In treatment of gonorrheal infection a larger dose is required.

Sulfanilamide will eradicate at least 90 per cent of uncomplicated infections of the urinary tract, and it is of value in treatment of infections with organisms of the genus Proteus. Fortunately, when sulfanilamide is used it is not necessary to depend on any particular p_H of the urine, although a dose of 10 grains (0.65 Gm.) of sodium bicarbonate usually is given with each dose of sulfanilamide. Complications associated with infections of the urinary tract usually decrease the efficacy of sulfanilamide as well as of other drugs; however, in cases of chronic prostatitis associated with bacillary infection the results obtained with sulfanilamide have been encouraging. Frequently, chronic prostatitis has disappeared in ten to fourteen days with this form of treatment. Sulfanilamide is not as effective against coccic as against bacillary infections, but it is definitely worth while. Headache, vertigo and lassitude occur almost invariably with the use of sulfanilamide. Fever, cyanosis or cutaneous eruption may also occur. Cook emphasized the importance of close observation, careful administration of the drug and careful regulation of the dose.

Vest, Harrill and Colston [49] stated that the introduction of sulfanilamide is the most important forward step yet made in the treatment of gonorrhea and other infections of the urinary tract.

Sulfanilamide may be only the forerunner of far more efficacious and satisfactory compounds, but with the vast problems yet to be elucidated concerning sulfanilamide itself years undoubtedly will be required to produce results such as Ehrlich predicted. From research in all fields, however, whether chemical, biologic or clinical, undoubtedly there will evolve the ideal remedy postulated by Ehrlich in 1913: "a remedy entirely innocuous in itself, which is not fixed by the organs

49. Vest, S. A.; Harrill, H., and Colston, J. A. C.: The Use of Sulfanilamide in Urological Infections, Tr. Southwest. Br., Am. Urol. A., 1937, pp. 127-150.

of the body but which would, however, strike the parasites with full intensity."

Hutchison [50] reported a series of 35 consecutive cases from the ward for venereal diseases in the Belvedere Hospital, between January 1935 and March 1938. The first 12 patients were treated with local applications only, the second 12 with a stabilized suspension of Ducrey bacilli (Dmelcos vaccine) and the remaining 11 with sulfanilamide. Each patient had a definite bubo, and some had a chancroid on the penis. None suffered from gonorrhea, and the blood serum of all gave a negative Wassermann reaction.

Treatment in all 35 cases was successful, and the most striking difference among the three groups was the reduction in the average duration of hospitalization from forty-six days to fifteen days. Of the 24 cases in which sulfanilamide was not given, aspiration was necessary in 20 and incision in 18. Of the 11 cases in which sulfanilamide was given, aspiration was required in only 2 and incision in none.

Although the number of patients so far treated with sulfanilamide is small, the evidence favors use of this drug in the treatment of bubo.

GLANDULAR THERAPY

With the use of gonadotropic substance from the urine of pregnant women, Thompson, Heckel and Bevan [51] have produced descent of 8 of 36 undescended testes (22 per cent) of 28 patients, varying in age from 1½ to 37 years.

By exclusion of 7 patients who were more than 15 years of age the incidence of successful results rose to 33 per cent. Testicular descent was not produced in any case if the patient was more than 12 years of age.

In all cases in this series in which descent took place, the testis was in the inguinal canal or at a lower level before treatment was started. In all successful instances in which the data were extensive enough to warrant conclusions, descent occurred within nine weeks.

In 8 cases in which operative procedures were carried out, after prolonged treatment with this material had failed to produce descent, anatomic factors which prevented descent were found. Even when descent did not occur, administration of the material, by increasing the size of the parts involved, seemed to make subsequent operative procedures less difficult.

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50. Hutchison, A.: Treatment of Bubo with Sulphanilamide, Lancet **1**:1047-1048 (May 7) 1938.

51. Thompson, W. O.; Heckel, N. J., and Bevan, A. D.: Influence of Anterior Pituitary-Like Principle on External Genitalia of Young Boys, J. Urol. **40**:145-153 (July) 1938. The preparation used was follutein (Squibb).

A striking result of the treatment was an increase in the size of the genitalia, which occurred in more than half the cases and was marked in more than a third. This increase was occasionally so marked that changes simulating premature puberty resulted.

Excessive genital growth may be prevented by avoiding long-continued treatment and by careful observation of the patient. Some regression in the size of the genitalia may occur when treatment is stopped.

Because of its stimulation of genital growth the material is also of value for use before operation for hypospadias, after operation for undescended testis when the testis has not been brought to a sufficiently low level and in the treatment of hypogenitalism.

Vest and Howard [52] reported the use of testosterone propionate in 6 cases of hypogonadism and in 2 cases of prepubertal boys. It seems to constitute a satisfactory replacement therapy for hypogonadism of the male human being. The authors have shown that it produces profound anatomic changes, resulting in the proportionate growth of the phallus, scrotum, seminal vesicles and prostate gland, as well as in development of hair in the pubic region, in the axillas and on the extremities. Other results have been laryngeal changes, the appearance of considerable prostatic secretion, ejaculation with coitus and marked changes in the skin. There have been, in addition, changes in general appearance and improvement in personality. Administration of the material has induced libido and potentia in cases in which these had not existed previously and has restored normal sexual life to a patient who was impotent after castration. No evidence of increase in tolerance to the drug has been noted.

PROGNOSIS OF UNILATERAL NEPHRECTOMY

Deming [53] stated that the expectancy of life of the unilaterally nephrectomized person depends (1) on the cause for which the kidney was removed, (2) on the condition of the remaining kidney and (3) on the social status of the patient. Certain operative procedures applicable in cases in which tuberculous or pyogenic infection exists are available; these procedures diminish the mortality and shorten the postoperative course. The young person whose kidney has been removed for other causes than malignant tumor has a normal expectancy of life. Marriage is permissible for those persons whose kidneys func-

52. Vest, S. A., Jr., and Howard, J. E.: Clinical Experiments with the Use of Male Sex Hormones, J. Urol. **40**:154-183 (July) 1938.

53. Deming, C. L.: The Future of the Unilaterally Nephrectomized Patient, J. Urol. **40**:74-82 (July) 1938.

tion normally for a reasonable period after nephrectomy. Pregnancy is permitted for all healthy women who have not harbored a malignant growth.

UROGRAPHY

Praetorius [54] called attention to the fact that the blood clots can be impregnanted by weak solutions of silver nitrate, such as might be used for lavage of the renal pelvis. Blood clots occasionally are a source of error in roentgenologic diagnosis, for they may be mistaken for stones. Several roentgenograms illustrated this.

Lateral pyelograms in 3 cases of perinephric abscess reported by Menville [55] showed a uniform anterior arclike displacement of the kidney and ureter on the affected side. Postoperative lateral pyelograms in the same cases disclosed that the kidneys and the ureters were in normal position and that there was no evidence of anterior displacement. A lateral pyelogram in a case of very early perinephric abscess gave evidence of minute, anterior displacement of the kidney and ureter.

Stevens [56] discussed roentgen examination of the kidney, with special reference to back flow and to injuries associated with retrograde pyelographic examination.

He stated that excretory urographic study furnishes sufficient data for exact diagnosis in a limited number of cases; in the others it must be supplemented by retrograde injections. The better visualization of the renal cortex after excretory as compared with that after retrograde urographic study is an important factor in the diagnosis of tumors of the kidney that do not involve or exert pressure on the renal pelvis or calices.

It is impossible to perforate a normal renal pelvis with an ordinary ureteral catheter. Extreme gentleness should be employed in catheterization of, and in injection into, the renal pelvis of infants and young children. Injury to the kidney and back flow are not uncommon in the course of retrograde pyelographic examination. Filling the renal pelvis to the point of discomfort is sometimes a dangerous procedure. The principal danger accompanying extravasation into the parenchyma of the kidney and in the various types of back flow lies in dissemination of infectious material. Extravasation into the renal parenchyma may

54. Praetorius, G.: Eine Irrtumsquelle bei Röntgenuntersuchungen der Niere, Ztschr. f. Urol. **32**:350-355, 1938.

55. Menville, J. G.: The Lateral Pyelogram as a Diagnostic Aid in Perinephric Abscess, J. A. M. A. **111**:231-233 (July 16) 1938.

56. Stevens, W. E.: Roentgenologic Examination of the Kidney with Special Reference to Backflow and Injuries Associated with Retrograde Pyelography, Tr. Am. A. Genito-Urin. Surgeons **30**:169-182, 1937.

be responsible for mistakes in diagnosis. Rupture extending through the capsule of the kidney is the most dangerous complication associated with retrograde pyelographic examination.

MULTIPLE MALIGNANT GROWTHS

Kretschmer [57] reported in detail 5 cases of multiple primary malignant tumor. In 3 cases the multiple tumors were in the urogenital tract, and in 1 case one was in the prostate gland and the other on the ear. In the first case 3 primary malignant tumors were present. Studies seem to indicate that the incidence of such tumors is greater in the United States than in Europe.

FORMATION OF BONE IN TRANSPLANTS FROM THE UROGENITAL TRACT

Abbott, Goodwin and Stephenson [58] found that the epithelial lining of the canine kidney, renal pelvis, ureter or any portion of the vesical mucosa (with the exception of that which covers the vesical trigon) when transplanted to a position within the sheath of the rectus abdominis muscle produced an epithelium-lined cyst, in connection with which true bone was formed.

The epithelial lining of the fundus of the bladder of the cat when transplanted in the same manner produced large, thin-walled cysts. Formation of bone did occur, but to a much less degree than when the dog was the experimental animal.

Epithelial transplants from the fundus of the bladder of a rabbit produced cysts but no bone.

Vesical mucosa from the fundus of the bladder of the guinea pig produced masses of epithelium, associated in 2 cases with formation of bone.

The mucous membrane of the vas deferens, fallopian tubes, uterus, vagina and rectum when transplanted produced cysts lined by their own particular type of epithelium but did not produce bone.

Removal of three parathyroid glands appeared to inhibit formation of bone after transplantation of epithelial grafts from the fundus of the bladder of the dog. This could be corrected by administration of calcium.

The investigators' results, therefore, demonstrate that the bone-forming potentiality of the various epithelial transplants cannot be assigned to sets of embryologic derivatives but should be attributed to

57. Kretschmer, H. L.: Multiple Primary Cancers, J. Urol. **40**:421-445 (Sept.) 1938.

58. Abbott, A. C.; Goodwin, A. M., and Stephenson, E.: Heterotopic Bone Formation Produced by Epithelial Transplants from Urogenital Tract of Dogs, Rabbits, Guinea-Pigs and Cats, J. Urol. **40**:294-311 (Aug.) 1938.

different types of epithelium: transitional epithelium can grow bone (renal pelvis, ureter and bladder); columnar epithelium (vas deferens, tubes, uterus and rectum) and stratified squamous epithelium (vagina) cannot.

DIABETES IN UROLOGIC SURGERY

Duff and Williams [59] stated that the patient in whom a genitourinary disturbance is complicated by diabetes should be cared for by a urologist and also by an internist, so that there will be good management of the patient's diet. Dehydration and severe ketosis are the only contraindications to urgent surgical operation. Absolutely sugar-free urine and low values for blood sugar are not essential before operation. The type of diabetes encountered in urologic practice usually is mild, and deaths should not be of diabetic origin. Insulin should be used cautiously, mainly for the purpose of combating dehydration and ketosis and to control severe glycosuria. If it is given until the urine is free of sugar and the value for blood sugar is low, it may cause dangerous hypoglycemia.

UROLOGIC DIAGNOSIS

Illustrative cases emphasize the fact that lesions of the urinary tract sometimes produce symptoms strongly suggestive of intra-abdominal disease.

Chute and Kelley [60] stated that this is not an everyday occurrence but added that it happens with sufficient frequency to make it advisable that the possibility of some pathologic condition of the urinary tract be kept in mind in the study of cases in which there are abdominal symptoms and the diagnosis is doubtful. In a fair number of Chute and Kelley's cases urinalysis and plain roentgenograms gave negative results. Therefore, since few patients are too ill to tolerate intravenous urographic examination this procedure and further urologic study, if indicated, should be carried out in any puzzling case in which abdominal symptoms are present even though urinalysis and plain roentgenograms do not give evidence of abnormality.

ADRENAL TUMORS

Walters and Kepler [61] reported 7 consecutive cases of tumor of the adrenal cortex in which recovery occurred after removal of the tumor. Symptoms produced by a tumor of the adrenal cortex depend on the

59. Duff, J., and Williams, F. W.: Diabetes in Surgical Urology, J. Urol. **40**: 446-451 (Sept.) 1938.

60. Chute, R., and Kelley, S. B.: Lesions of the Urinary Tract Producing the Symptoms of Intra-Abdominal Disease, J. Urol. **39**:683-691 (May) 1938.

61. Walters, W., and Kepler, E. J.: Adrenal Cortical Tumors and Their Treatment; A Study of Seven Operated Cases, Ann. Surg. **107**:881-896 (June) 1938.

sex and age of the patient at the time the tumor begins to function. These tumors are encountered most frequently among women and are characterized by variable changes in secondary sexual characteristics, such as cessation of menstruation, occasional hypertrophy of the clitoris, abnormal growth of hair of masculine distribution and characteristic lesions of the skin, such as a florid complexion accompanied by acne and purplish striations. In girls, tumors of the adrenal cortex tend to produce precocious puberty, more masculine than feminine in character. The disease seldom occurs among males. The clinical picture is not pathognomonic. Similar clinical pictures may result from certain tumors of the gonads, from hyperplasia of the adrenal cortex with or without thymic tumors and from various intracranial lesions not directly involving the pituitary body.

Routine laboratory studies have been of little aid in differential diagnosis, although the presence of a high concentration of estrogenic substance in the urine is suggestive of carcinoma of the adrenal cortex provided pregnancy is excluded. Injection of air about the adrenal gland has been of aid in localizing some adrenal tumors in some cases.

MacKenzie and McEachern [62] reported a case of paroxysmal hypertension due to adrenal pleochromocytoma. The patient, a man 29 years of age, had suffered from attacks of increasing severity for eighteen months. The attacks lasted two to ten minutes and were characterized by nausea, substernal distress, generalized and localized headache, tremor, pallor and numbness of the extremities. They were followed by exhaustion. Attacks were produced by exercise, change of posture and abdominal massage. They were intensified during fasting and were relieved by taking food. During an attack there were a great rise of the brachial and retinal blood pressure, slowing of the cardiac rate, disappearance of the radial pulse, drop in cutaneous temperature, increase in the number of lymphocytes in the blood stream and glycosuria. In the intervals between attacks the blood pressure was normal and there was no evident cardiovascular abnormality. Plain roentgenograms, intravenous pyelograms and massage over the adrenal glands failed to demonstrate the site of the tumor.

Exploration of the region of the left adrenal gland did not reveal a tumor. At the same sitting the opposite side was explored, and an encapsulated tumor of the weight of a golf ball (24 Gm.) was removed from the right adrenal medulla. It proved to be a typical pleochromocytoma, and an extract of it contained a large amount of epinephrine.

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62. MacKenzie, D. W., and McEachern, D.: Tumor of Medulla of Adrenal (Adrenal Pleochromocytoma) with Removal and Relief of Paroxysmal Hypertension, J. Urol. **40**:467-476 (Oct.) 1938.

Further attacks did not occur after operation, and four and one-half months later the patient reported himself entirely well.

Review of the literature showed that some 20 patients have been operated on; including the 1 whose case was reported by MacKenzie and McEachern, 5 died from shock or complications. Fifteen recovered and had remained free of attacks. Evidence indicated that the paroxysms of hypertension are due to intermittent hypersecretion of epinephrine into the blood stream by the chromaffin tumor of the adrenal gland.